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On examination the patient showed normal physical development, but there was marked pallor of the skin and the visible mucous membranes with an icteric tinge in the conjunctivae and a slight lemon-yellow discoloration of the skin. There was marginal gingivitis with caries of the remaining four lower incisor teeth. The distribution of the papillae on the tongue was normal. The fundi and retinal blood-vessels were normal. Exploration of the right maxillary antrum showed the presence of pus. The pulse-rate was regular with a slight bradycardia (64), and the blood-pressure was 150/90. The apex-beat was displaced just below and internal to the nipple line four inches from the midline in the fifth intercostal space. Moderate cardiac enlargement was present on percussion. A soft systolic murmur was heard in the mitral and pulmonary areas and the second pulmonary sound was accentuated. General fluoroscopic examination of the chest was normal apart from slight to moderate cardiac enlargement. On abdominal examination the liver and spleen were not palpable, a left inguinal hernia was present. There was no enlargement of lymphnodes in the cervical, axillary, or inguinal regions. General neurological examination was normal, apart from exaggeration of the deep reflexes.

Laboratory investigations The red cells were 2,610,000 per c mm, haemoglobin (Sahli) 55 per cent, colour index 1.06, and white cells 5,200 per c mm. There was moderate anisocytosis and poikilocytosis and slight polychromatophilia. The differential leucocyte count showed polymorphonuclear neutrophile cells 42 per cent, eosinophiles 4 per cent, lymphocytes 45 per cent, and large mononuclear cells 9 per cent. The blood-platelets were 146,000 per c mm and reticulocytes 16 per cent. A Price-Jones curve (performed on November 7, 1945, when the red-cell count was 1,815,000 per c mm and the haemoglobin 29 per cent) showed mean cell diameter 8.14μ , standard deviation 0.8994, coefficient of variation 11.05 per cent, megalocytosis 25 per cent, and microcytosis 2 per cent. The haematocrit reading was 16 per cent, mean corpuscular volume $88 \text{ c } \mu$, and mean corpuscular haemoglobin concentration 29 per cent. The myelogram showed a marked hyperplasia of the erythropoietic tissue, normoblastic in type.

Myeloid-erythroid ratio 0.9:1

Proerythroblasts	3	} per cent
Early normoblasts	15	
Late normoblasts	23	
Myelocytes	6	
Leucocytes	32	
Lymphocytes	20	
Monocytes	1	

Blood group O, Rh positive. Blood Wassermann reaction negative. Kahn test negative. Van den Bergh indirect reaction, bilirubin 2.5 mg per 100 c.c. Fragility of red blood cells (Creed, 1938), haemolysis 100 per cent at 0.28 per cent sodium chloride, 80 per cent at 0.32 per cent, 70 per cent at 0.36 per cent, 50 per cent at 0.40 per cent, 20 per cent at 0.44 per cent, 8 per cent at 0.48 per cent, and nil at 0.52 per cent. Donath-Landsteiner reaction negative. Titre of cold agglutinin 1:4. The serum-calcium was 8.7 mg per 100 c.c., serum-phosphorus 3.36 mg per 100 c.c., and serum-cholesterol 147 mg per 100 c.c. The serum-protein was 6.25 gm per 100 c.c., albumin 4.2 gm per cent, and globulin 2.05 gm per 100 c.c. The urine was alkaline in reaction, and no sugar or albumin was present. A fractional test-meal showed total achlorhydria after histamine stimulation. Tests for occult blood in faeces were negative.

Haemoglobinuria was first noted on February 15, 1944, while the patient was undergoing clinical investigation in hospital, and persisted until April 1, 1944.

Discoloration of the urine, due to free haemoglobin, was present in all specimens of urine voided, day and night, over this period. At intervals during this time paroxysmal attacks of pallor of the fingers were noted, but reactive hyperaemia and cyanosis were absent. No local or systemic reactions were noted. The urine showed the presence of free haemoglobin, which was confirmed by spectroscopic examination. The urine was alkaline in reaction with albumin ++ and no sugar. The urinary sediment was free from red blood cells. The faeces were deeply pigmented. During this period haemoglobinaemia was a constant finding and

TABLE I

Effect Produced on Haemolytic Activity of Serum by Dilution with (a) Saline and (b) Serum Heated to 56° C for 15 Minutes

Serum* (%)	Saline (%)	Haemolysis of patient's red cells after	Serum (%)	Serum heated to 56° C for 15 min	Haemolysis of patient's red cells after
		1 hr at 37° C		(%)	1 hr at 37° C
50	50	Trace	50	50	Nil
75	25	+	75	25	Nil
90	10	+	90	10	Trace
95	5	+	95	5	+
100	0	+	100	0	+

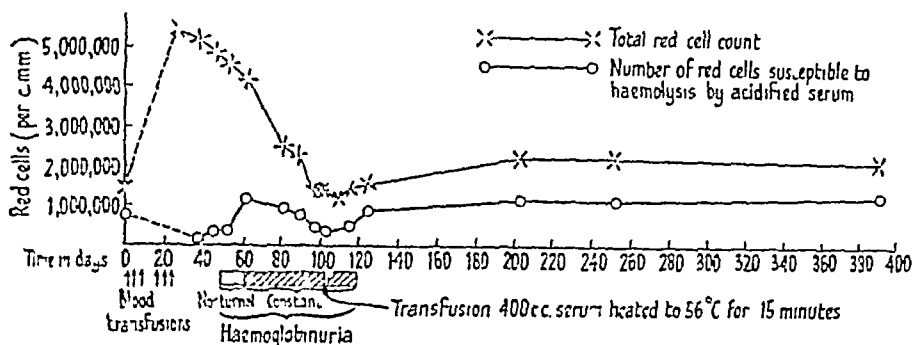
* All serum used was collected from a normal Group O subject on the day of the experiment and adjusted to pH 6.6 by addition of N/3 hydrochloric acid before use. When the serum was heated this was done before the pH adjustment.

The volumes used were 0.4 c.c. serum or serum saline mixture, and 0.02 c.c. of the patient's red cells.

marked haemolysis occurred when a sample of blood was incubated immediately after collection. The patient's red cells gave a positive result in Ham's haemolysis test with acidified serum (Ham, 1939). Subsequently the red cells were shown to be susceptible to haemolysis by a heat-labile component of human serum. This haemolytic substance was present at low titre in the patient's serum and in serum from normal persons. Its titre fell rapidly when the serum was stored. Serum left for one week in the ice-box no longer had haemolytic activity. Haemolysis was produced over the pH range 6.06 to 7.18, and was maximal at 6.6. The above findings are characteristic of the Marchiafava-Micheli syndrome.

Heating serum to 56° C for 15 minutes destroyed the haemolytic activity. Heated serum was found to have an inhibitory effect on the haemolytic activity of unheated serum (Table I). This inhibitory effect was not transferred to the patient's red cells by incubating them in heated serum, because such cells when washed in saline were again as equally susceptible to the haemolytic effect of unheated serum as cells not so treated. The patient's red cells were not all susceptible to haemolysis. When the same sample of cells was subjected to haemolysis by repeated changes of serum, a stage was reached when no further haemolysis occurred and some unaffected cells remained. Except after transfusions the percentage of red cells susceptible to haemolysis was found to remain relatively constant at 50 to 60 per cent. over a prolonged period (Table III). The figure was estimated as follows. An approximately three per cent suspension of the patient's red cells was prepared in saline, thoroughly mixed, and the cells counted in a haemocytometer. Two c.c. of the suspension were transferred to a graduated centrifuge tube. The cells were centrifuged, the saline removed, and the cells re-suspended in fresh serum which had been acidified by the addition of five per cent N/3 hydrochloric acid. After one hour's incubation in a water-bath

at 37°C the tube was centrifuged, the serum removed, and the cells re-suspended in acidified serum. The process was repeated until no further haemolysis occurred. Usually three changes of serum sufficed. The volume of fluid was then adjusted to the original mark and the residual cells thoroughly mixed and counted. To determine if susceptibility to haemolysis depended on the age of the cells, reticulocyte counts were carried out on samples of the patient's red cells before and after haemolysis. No significant alteration from the initial figure of 15 per cent of reticulocytes was obtained after maximal haemolysis. From this



Effect of blood transfusions on the patient 'Time in days' commences on 23.2.1946

it was concluded that susceptibility to haemolysis was not a function of the age of the cell.

To investigate the possibility that the abnormality of the erythrocytes was due to sensitization by a haemolytic antibody, the patient's red cells were tested with rabbit anti-human globulin serum (Coombs, Mourant, and Race, 1940). Agglutination did not occur and susceptibility of the cells to subsequent haemolysis by acidified human serum was not altered. In the absence of haemoglobinuria the presence of methaemalbumin in the patient's serum was demonstrated by means of the reversion spectroscope. Schumm's ammonium-sulphide test, as described by Fairley (1941), was strongly positive. Throughout the period of observation, haemosiderinuria was a constant finding both during and between the attacks of haemoglobinuria.

Progress The attack of haemoglobinuria noted above followed the daily administration of 60 gr. of iron and ammonium citrate with 60 minims of dilute hydrochloric acid and appeared on the eighth day of treatment. On questioning the patient it was discovered that a similar discoloration of the urine had followed the therapeutic administration of iron on at least five occasions in the past and was associated with gastric flatulence and indigestion. The change in colour of the urine appeared about seven to ten days after the commencement of treatment and persisted for a period of about ten days. Paroxysmal pallor of the fingers had been present for many years and was most marked in the morning, it was not constantly present throughout the period of haemoglobinuria and frequently appeared in its absence. In order to test the relationship between iron therapy and haemoglobinuria, on November 4, 1944, ferrous sulphate in doses of 60 gr. daily with 30 minims of dilute hydrochloric acid thrice daily was administered. Haemoglobinuria appeared seven days later and although therapy was discontinued the haemoglobinuria persisted for three weeks. At this stage it was considered that the haemoglobinuria was produced by the administration of hydrochloric acid, but subsequent observations indicated that it was more likely that iron was the causative factor. The first obser-

vation was made on February 23, 1945, when haemoglobinuria was noted; 16 days previously the patient had taken one tablet (5 gr) of ferrous sulphate daily for 14 days. One month later a simple tonic mixture was prescribed as a placebo. This was not available and the pharmacist substituted a mixture of iron and ammonium citrate (15 gr. three times daily). Six days later discoloration of the urine became apparent and persisted for nine days. These four episodes of haemoglobinuria were the only attacks which took place during a period of 24 months' observation from February 15, 1944, to February 15, 1946.

TABLE II

Date	Red cells (per c.mm.)	Haemoglobin (%)	Other observations
21 7 42	2,570,000	51	
13 1 43	2,740,000	54	
2 2 44	2,610,000	55	White cells 5,200 per c.mm.
18 2 44	2,470,000	54	Reticulocytes 16 %
7 3 44	2,440,000	33	Reticulocytes 20 %
31 10 44	2,250,000	34	
27 10 45	2,330,000	36	White cells 5,900 per c.mm.
7 11 45	1,815,000	29	Reticulocytes 16 %
10 11 45	1,700,000	29	
14 11 45	1,675,000	31	
17 11 45	1,975,000	40	
21 11 45	1,940,000	35	Reticulocytes 15 %
28 11 45	1,887,000	30	
19 12 45	2,000,000	30	
16 1 46	1,770,000	28	White cells 7,750 per c.mm.
23 2 46	1,430,000	25	

Therapy with iron had no favourable influence upon the blood picture during the period under review. From January 28, 1944, to January 16, 1946, there was a slowly progressive diminution in the total red-cell count and haemoglobin percentage, as indicated by Table II.

Since a review of the available literature indicated that there was no effective therapy for the Marchiafava-Micheli syndrome, the patient received no medicine apart from the four test administrations of iron noted above. However, in February 1946 the serious deterioration in the blood count (Table II) accompanied by a pronounced clinical deterioration in the condition of the patient prompted us to test the value of repeated blood-transfusions. Between February 26 and March 21, 1946, the patient was given four litres of whole blood in a series of six transfusions. The red cell count was raised to 5,440,000 per c.mm., and haemoglobin to 90 per cent. The subsequent haematological findings are shown in Table III. The pre-transfusion level of red cells was reached approximately 70 days after the final transfusion. Haemoglobinuria appeared 24 days after the final transfusion. The haemoglobinuria was confined to the morning urine for 11 days. This was the only occasion on which nocturnal haemoglobinuria alone was observed in this patient. After 11 days of nocturnal haemoglobinuria only, the haemoglobinuria became constant and was present in all specimens passed both day and night. The amount of haemoglobin present in the day specimens was approximately equal to that present in the specimens passed at night and in the early morning. The constant haemoglobinuria lasted for 58 days, with the exception of a period of about 36 hours after a transfusion of 400 c.c. of serum which had been previously heated to 56° C for 15 minutes. This transfusion was given on the morning of the 42nd day of constant haemoglobinuria. The next specimen of urine passed, at 3 p.m., was burgundy-coloured like all specimens for the previous 41 days. A specimen passed at

6 p.m. and all the urine passed on the following day was yellow in colour and showed no macroscopic evidence of haemoglobin. A trace of haemoglobin was demonstrated in all these specimens by the benzidine test. Frank haemoglobinuria again appeared on the morning of the second day after the serum-transfusion and remained constant for 14 days. After the blood-transfusions the number of red cells in the patient's circulation susceptible to haemolysis by acidified serum fell to a very low level. This level rose rather rapidly until the onset of constant haemoglobinuria, after which it fell slowly. It rose again when

TABLE III

Date	Red cells (per c mm.)	Red cells susceptible to haemolysis (per c mm.)	Haemoglobin (%)	Reticulocytes (%)
23 2 46	1,430,000	763,000	25	13
21 3 46	5,440,000		90	
1 4 46	5,150,000	176,000	96	0.5
9 4 46	4,910,000	335,000	100	
16 4 46	4,550,000	346,000	92	
25 4 46	4,190,000	1,173,000	83	
14 5 46	2,515,000	956,000	62	
21 5 46	2,205,000	772,000	56	25
30 5 46	1,390,000	431,000	40	
1 6 46	1,410,000		38	26
3 6 46	1,400,000	336,000	39	
5 6 46	1,390,000		35	
11 6 46	1,190,000		28	
17 6 46	1,480,000	444,000	39	
26 6 46	1,530,000	872,000	35	
12 9 46	2,220,000	1,177,000	43	14
31 10 46	2,220,000	1,132,000	40	22
21 3 47	2,130,000	1,260,000	41	13

the haemoglobinuria ceased and subsequently has remained remarkably constant at about the pre-transfusion level (Figure). The patient has been under observation up to March 1947, and no further attack of haemoglobinuria has been noted.

Discussion

The case here described showed the characteristic finding of the Marchafava-Michel syndrome in that there was an abnormality of the red cells which rendered them susceptible to haemolysis by some normal constituent of human serum within the physiological range of pH. Certain unusual clinical and laboratory findings were noted.

1 Haemoglobinuria was not observed to occur spontaneously, but only after iron therapy and blood-transfusions. Nocturnal haemoglobinuria alone was observed only on one occasion, during the first few days after a blood-transfusion.

2 Preliminary cooling of the washed cells was not necessary to permit of lysis taking place, nor did such cooling result in an increased degree of lysis as was found by Dacie, Israëls, and Wilkenson (1938).

3 Serum heated to 56° C. was found to exert an inhibitory effect on haemolysis. In general this finding is contrary to the experience of most other workers.

Lescher and Osborn (1939) 'observed no inhibitory effect in heated serum since addition of fresh unheated serum of patient or of a control to the suspension of the patient's red blood cells in serum which had been heated to 56° C caused lysis'

Ham and Dingle (1939) gave figures for the degree of haemolysis which they obtained with mixtures of acidified fresh and heated serum. Fifty per cent fresh serum and 50 per cent heated serum gave 19 per cent haemolysis, 30 per cent fresh and 70 per cent heated, 10 per cent haemolysis, and 20 per cent fresh and 80 per cent heated, 8 per cent haemolysis. These workers found that the haemolytic activity of mixtures of fresh and heated serum was approximately proportional to the amount of complement present. Dacie, Israëls, and Wilkinson (1938) speaking of plasma that had been heated to 56° C for 30 minutes stated that 'Such plasma added to red cells which had been previously allowed to absorb lysin proved completely inhibitory to subsequent lysis'. Our findings were that heated serum when mixed with fresh serum had an inhibitory effect on haemolysis, but that the patient's red cells which had been incubated in heated serum and then washed in saline were just as susceptible to haemolysis as red cells not so treated. Heated serum was shown to have a transient inhibitory effect on haemoglobinuria *in vivo*. A period of constant haemoglobinuria was interrupted for approximately 36 hours by a transfusion of 400 c.c. of heated serum. Dacie and Firth (1943) gave a series of six transfusions of stored serum to a case. Each transfusion was immediately followed by a transient period of marked haemoglobinaemia and haemoglobinuria. The reason of the inhibitory effect of heated serum *in vitro* and *in vivo* is not apparent. Bawden and Kleczkowski (1942) studied the effect on serological reactions of heating anti-sera. They found that heating serum resulted in a union between antibody globulin and the albumin fraction producing mixed complexes which had an inhibitory effect on certain precipitation reactions. The degree of heat necessary to produce this effect, 75° to 80° C, was, however, much greater than anything we employed; they found further that the presence of such mixed complexes did not inhibit complement fixation reactions.

Dameshek and Schwartz (1938) and Ham and Dingle (1939) considered that the abnormality of the red cells was due to the presence of a lysin which becomes attached to the cells and sensitizes them. Evidence of such a lysin would be adduced if the red cells were agglutinated by an anti-human-globulin serum. This did not occur in our case.

The apparent connexion between iron therapy and haemoglobinuria observed in our patient has not, so far as we are aware, been evident in any of the previously recorded cases. Most of Ham's patients (personal communication) have received ferrous sulphate as a continuous form of therapy for periods of years at a time. Their episodes of haemoglobinuria were never attributed to this treatment. In the patient we have described there appears to be at any given period a critical level of red cells that can be tolerated, any increase above this level resulting in rapid haemolysis of the excess cells and haemoglobinuria. We are unable to suggest any reason for this.

Summary

1. A case of the Marchiafava-Micheli syndrome showing unusual features is described

2 The patient was observed for a period of three years, and five attacks of haemoglobinuria occurred during this time, four of these followed iron therapy and one followed blood-transfusions

3. A proportion of the patient's erythrocytes was susceptible to haemolysis by acidified human serum This proportion tended to remain relatively constant

4 Normal human serum heated to 50° C was shown to have an inhibitory effect on haemolysis

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ANOMALIES OF INTESTINAL ABSORPTION OF FAT

II THE HAEMATOLOGY OF IDIOPATHIC STEATORRHOEA¹

By W T COOKE, A C FRAZER, A L P PEENEY,
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With Plate 1

THIS paper presents the haematology of 45 cases of idiopathic steatorrhea, together with such observations that may shed some light on the aetiological factors concerned. The diagnosis of the cases has been made from consideration of the history, the presence of a characteristic haematological and abnormal electrolyte picture, excess faecal fat, flat glucose tolerance and chylomicrograph curves, and low fasting serum lipids. In 42 patients the presence of a fat absorption defect was determined by a fat balance technique (Cooke, Elkes, Frazer, Parkes, Peeney, Sammons, and Thomas, 1946), in the remaining three cases the diagnosis had been made elsewhere. In six cases intestinal intubation was carried out, in the remaining living cases the possibility of fibrous pancreatitis has not been eliminated. There were 23 male and 22 female patients whose ages when first seen are shown in Table I.

TABLE I

Age (years) when first seen	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79
Number of cases		3	8	12	9	9	2	2

Haematological Findings

The haematological findings in 26 patients, who have been under close supervision, are given in Table II. The seven fatal cases have been listed separately (Table III). The remaining 12 patients, who have been under observation for less than 12 months, or who have had blood counts on one occasion only, showed essentially similar findings. Thirty-three cases had red-cell counts above 2,500,000 per c mm and haemoglobins above 50 per cent, the remaining 12 had either red cells or haemoglobin, or both, below these levels. These findings are similar to those noted by Witts (1932), Bennett, Hunter, and Vaughan (1932), Thaysen (1932, 1935), Moore, O'Farrell, Geraghty, Hayden, and Moriarty (1936), Hotz and Rohr (1938), and Snell (1939). When first seen, only two patients had white-cell counts above 10,000 per c mm, in each case associated with infection, and 10 showed a leucopenia, the lowest count being 1,050 per

¹ Received July 16, 1947

Main Haematological and Relevant Features of 26 Patients who have been under Regular Supervision for One to Five Years. In

all Cases the Initial Blood Count and the Most Recent Count are given, the Highest Levels attained are also included

Case	Sex and age	Age at onset	Presenting symptoms	Date	Retic cells (millions per cmm)	Haemo-globin (%)	Colour index	White cells (per cmm)	Free HCl	Serum bilirubin (mg per 100 c.c.)	Packed cell volume (%)	Mean corpuscular volume (c μ)	Mean corpuscular haemoglobin concentration (%)
1	F 33	2	Loose stools for 5 years	5.6.44	4.69	56	0.8	3,250	Present	Zero	33	70.36	23.33
				22.6.46	1.57	68	0.75				37	80.96	25.4
				22.11.44	1.9	52	1.37	3,250	Present	0.05	40	88.6	31.7
2	F 64	64	Weakness and stiffness of legs for 3 months	18.6.46	4.51	92	1.01		Present	0.5	23	67.8	19.2
				10.3.44	3.39	32	0.49	7,000	Present		33.5	70.3	27.2
				4.7.44	5.62	80	0.71						
3	F 48	12	Loose stools for 25 years	7.5.46	4.22	66	0.78		Present	Zero			
				18.10.42	2.37	84	1.02	5,150	Present				
				5.2.44	4.1	68	0.88				31	80.5	30.3
4	F 36	5	Intermittent diarrhoea and glossitis for 12 months	20.1.46	3.85	78	1.4	6,400	Present	Zero	37.5	133	28.8
				20.4.43	2.82	102	1.26				45.5	115.7	27.9
				16.3.44	4.07	92	1.18			0.1	30.5	132.6	29.8
5	F 21	9	Severe cramps for 4 years	21.6.46	3.93	65	1.43	7,800	Present		34	105.5	30.86
				18.1.44	2.3	82	1.05						
				27.4.44	3.94	76	1.10	3,450	Present	Zero	35	119.8	30.7
6	F 33	32	Lassitude, sore tongue, and anaemia for 1 year	27.46	3.34	78	1.16				27	125.5	30.7
				17.2.42	4.04	84	1.04						
				18.11.43	2.02	78	1.34						
7	F 46	45	Sore tongue, loose stools, and tetany for 6 months	18.6.46	2.15	60	1.39	4,550	Present	Zero	31	106.1	30.29
				12.10.43	2.15	70	1.05				43.5	102.6	28.9
				1.2.44	3.58	68	1.17	5,200	Absent*	Zero	45	95.9	28.2
8	M 54	54	Loose stools and loss of weight	27.5.46	2.92	81	0.98		Absent	0.6	37	91.8	32
				4.11.43	4.24	92	1.08				30.5	114	30.8
				30.4.46	4.69	84	1.05						
9	M 50	20	Lassitude for 1 year	3.5.43	4.03	84	1.28	4,500	Present	Zero	39	97	28.32
				17.1.44	2.66	68	1.08				135.1	34.7	
10	M 47	Childhood	Excessive lassitude and loss of weight for 2 years	20.11.45	3.80	84	1.08	5,600	Present				
				22.1.45	2.92	38	0.65				41.5	120.6	28.6
				15.3.46	3.33	70	1.06				34	102.1	28.4
11	F 65	20	Breathlessness for 6 months	18.4.45	5.01	96	0.96						
				2.7.46	4.02	80	0.99		Present	0.4			
				20.1.45	1.53	48	1.55						
				24.7.45	3.58	92	1.28						
12	M 53	Childhood	Loss of weight for 12 months	15.3.46	3.44	86	1.25						
				30.4.43	3.33	84	0.84		Present	Zero	44	88.1	29.2
				4.8.43	5.11	94	0.94				17.5	110	33
13	M 16	Infancy	Recurrent sore mouth and diarrhoea for 6 years	12.6.46	4.09	94	1.22	3,400	Present	1.05			
				23.3.43	1.58	30	1.11						
				18.4.44	4.6	102	1.11						
14	M 51	5	Loss of weight and lassitude for 2 years	18.4.46	3.22	88	1.37						

15	M 26	14	Weakness and diarrhoea for 2 months	8 2 41	2 21	58	1 31	3,450	Present	Zero	44	101 0	29 5
				3 12 45	5 18	104	1 08	9,500			45	98 9	28 2
16	M 33	28	Diarrhoea for 4 weeks	23 6 43	3	86	1 42	3,700	Present	0 85			
				24 5 40	4 55	92	1 05						
17	F 57	47	Diarrhoea and abdominal pain for 2 years	31 7 44	2 59	74	1 42	4,550	Absent*	Zero	43 5	95	30 4
				12 7 45	5 03	100	0 89	7,100					
				4 4 46	4 58	96	1 04						
18	M 41	Infancy	Diarrhoea and sore tongue for 1 year	25 11 43	4 55	90	0 98	6,200	Absent	Zero			
				24 10 44	4 77	96	1 02						
				19 11 46	5	102	1 02						
19	F 46	7	Weakness and sore tongue for 1 year	25 2 44	3 77	82	1 09	5,800	Absent*	Zero	46	92	30 6
				24 3 44	4 55	92	1 01				41	100 0	28 3
				27 4 6	3 95	76	0 96				35	88 6	20 9
20	F 33	12	Lassitude for 12 months	31 7 43	4 36	62	0 71	3,450	Present	0 3			
				15 7 46	3 92	62	1 17						
21	F 52	?	Lassitude and backache for 6 months	10 10 45	3 07	55	0 9	6,800	Present	Zero	20	94 46	26 2
				9 4 46	3 9	76	0 97	8,650					
				16 7 46	3 45	66	0 95						
22	M 49	?	Diarrhoea for 8 years	10 1 46	3 48	68	0 93	4,050	Present	Zero			
				4 2 46	4 21	78	0 93						
				14 5 46	4 29	84	0 98				30 5	100 3	24 2
23	F 26	Infancy	Intermittent diarrhoea for 5 years	27 2 45	3 35	80	1 2	8,500	Present	0 8	41	95 5	28 5
				24 5 46	3 46	82	1 19	8,350			40	106 3	29 40
24	F 39	?	Pyrexia and lassitude for 1 month	25 10 45	2 86	54	0 94	6,050	Present	Zero	39	112 7	29 03
				15 6 46	3 75	76	1 01						
25	M 20	Infancy	Recurrent sore tongue for 5 years	11 1 43	4 95	92	0 93	8,050	Present	Zero	41	84 1	29 6
				20 5 46	4 87	88	0 91	5,350			35	90 9	23 7
26	F 35	20	Intermittent diarrhoea for 5 years	27 1 45	3 85	90	0 78	3,650	Present	Zero			
				20 3 46	4 07	96	1 18						

TABLE III

Fatal Cases

M 37	35	Latitude for 2 years	5 4 45	1 91	46	1 21	6,000	Present	0 8
M 33	21	Breathlessness for 6 months	2 6 44	3 45	88	1 27	7,750	Present	0 55
M 51	49	Diarrhoea and loss of weight for 2 years	10 10 42	2 5	70	1 4	9,050	Absent	Zero
			11 4 44	3 13	80	1 27	2,700		
M 54	41	Loss of weight and loose stools for 10 weeks	4 1 43	4 54	98	1 09	11,250	Absent	
			14 1 43	3 65	92	1 27	9,500		
M 43	43	Diarrhoea for 6 months	3 9 43	3 25	90	1 38	4,800	Present	1 1
			10 9 43	3 12	84				
M 33	5	Weakness and diarrhoea for 4 years	14 1 41	4 36	84	0 06	11,550	Present	0 2
F 70	65	Attacks of diarrhoea for 5 years and loss of weight for 8 months	13 3 44	3 8	100	1 31	5,300	Present	Zero
			16 9 44	3 35	90	1 34			
							41	112	29 6
							28	103	34
							30 5	136	29

Haemoglobin scale (Haldane), 100 per cent = 13.8 gm per 100 c.c.

* Indicates absence of free hydrochloric acid after histamine

Main Haematological and Relevant Features of 26 Patients who have been under Regular Supervision for One to Five Years In all Cases the Initial Blood Count and the Most Recent Count are given, the Highest Levels attained are also included

TABLE 11

Case	Sex and age	Age at onset	Presenting symptoms	Date	Red cells per c.mm.)	Hemo- globin (%)	Colour index	White cells (per c.mm.)	Free HCl	Serum bili- rubin (mg. per 100 c.c.)	Packed cell volume (%)	Mean corpus- cular volume (c ³)	Mean corpus- cular haemo- globin concen- tration (%)
1	F 33		Loose stools for 5 years	5.6.44	4.00	56	0.6	3,250	Present	Zero	33	70.36	23.33
2	F 64	64	Weakness and stiffness of legs for 3 months	22.11.44	1.57	68	0.75				37	80.96	25.4
3	F 48	12	Loose stools for 25 years	18.6.46 10.3.44 4.7.44	4.51 3.30 5.62	92 101 80	1.01	7,000	Present	0.65	40	88.6	31.7
4	F 36	5	Intermittent diarrhoea and glossitis for 12 months	18.10.42 5.2.44	4.22 4.1	66 84	0.78	5,150	Present	Zero	33.5	70.3	27.2
5	F 21	0	Severe cramps for 4 years	26.1.46 20.4.43 15.3.44	3.85 2.82 4.07	69 78 102	0.88	6,400	Present	Zero	31	80.5	30.3
6	F 33	32	Lassitude, sore tongue, and anaemia for 1 year	21.5.46 18.1.44 27.4.44	3.03 2.3 3.04	92 66 82	1.18	7,800	Present	0.1	45.5	115.7	27.0
7	F 46	45	Sore tongue, loose stools, and tetany for 6 months	17.2.42 18.11.43	3.22 4.04	70 84	1.19	3,450	Present	Zero	34	105.5	30.89
8	M 54	54	Loose stools and loss of weight	18.6.46 12.10.43 1.2.44	2.92 2.15 3.58	78 60 76	1.34	4,550	Present	Zero	35	119.8	30.7
9	M 50	20	Lassitude for 1 year	27.5.46 4.11.43	2.02 4.24	68 91	1.05	5,200	Absent*	Zero	27	125.5	30.7
10	M 47	Child hood	Excessive lassitude and loss of weight for 2 years	30.4.46 3.6.43	4.09 4.03	92 84	1.08		Absent	Zero	31	106.1	30.29
11	F 65	20	Breathlessness for 6 months	20.11.45 22.1.45 18.4.45	2.86 2.92 5.01	68 84 96	1.28	4,500	Absent	0.6	45	95.9	28.2
12	M 53	Child hood	Loss of weight for 12 months	27.4.6 20.1.45	4.02 1.53	80 48	0.99	5,600	Present	Zero	37	91.8	32.8
13	M 16	Infancy	Recurrent sore mouth and diarrhoea for 6 years	23.7.46 16.3.46 30.4.43	4.02 3.58 3.33	80 92 70	0.99		Present	0.4	30.5	114	30.8
14	M 51	5	Loss of weight and lassitude for 2 years	12.0.46 23.3.43 18.4.44 4.7.46	4.99 1.58 4.6 3.22	94 30 102 88	0.94	3,400	Present	1.95	39	97	28.32
												135.1	34.7
												120.6	28.6
												102.1	29.4
												88.1	20.2
												110	33

15	M 26	14	Weakness and diarrhoea for 2 months	8 2 41 3 12 45	2 21 5 18	58 104	1 31 1	3,450 9,500	Present	Zero	44 45	101 0 98 0	20 5 28 2
16	M 33	28	Diarrhoea for 4 weeks	17 5 46 23 6 43	4 33 3	84 86	1 08 1 42	3,700	Present	0 65			
17	F 57	47	Diarrhoea and abdominal pain for 2 years	24 5 46 31 7 44	4 55 2 59	92 74	1 05 1 42	4,550 7,100	Absent*	Zero			30 4
18	M 14	Infancy	Diarrhoea and sore tongue for 1 year	12 7 45 4 4 46	5 03 4 68	100 96	0 00 1 04	6,200	Absent	Zero	43 5	95	
19	F 46	7	Weakness and sore tongue for 1 year	25 11 43 24 10 44	4 55 4 77	90 96	0 98 1 02	5,800	Absent*	Zero	46 41	92 109 6	30 6 28 3
20	F 33	12	Lassitude for 12 months	10 11 46 26 2 44	5 2 7 46	102 82	1 02 1 01	3,450	Present	0 3	35	88 6	20 9
21	F 52	?	Lassitude and backache for 6 months	24 3 44 2 7 46	4 55 3 05	92 76	0 98 0 06	6,800 8,650	Present	Zero	20	94 46	26 2
22	M 40	?	Diarrhoea for 8 years	10 10 45 9 4 46	3 07 3 0	55 76	0 9 0 97	4,050	Present	Zero	36 5 41	100 3 95 5	24 2 28 5
23	F 26	Infancy	Intermittent diarrhoea for 5 years	16 7 46 10 1 46	3 45 3 48	66 66	0 95 0 05	8,500	Present	0 8	40 30	106 3 112 7	20 20 03
24	F 39	?	Pyrexia and lassitude for 1 month	4 2 46 14 5 46	4 21 4 20	78 84	0 93 1 2	8,350	Present	Zero			
25	M 20	Infancy	Recurrent sore tongue for 5 years	27 2 45 24 5 46	3 35 3 46	80 82	1 2 1 10	6,650	Present	Zero	41 35	84 1 90 9	20 6 23 7
26	F 35	20	Intermittent diarrhoea for 5 years	25 10 45 15 6 46	2 86 3 75	54 76	0 94 1 01	8,050	Present	Zero			

TABLE III

Total Cases

35	M 37	35	Lassitude for 2 years	5 4 45	1 01	46	1 21	6,000	Present	0 8			
36	M 31	21	Breathlessness for 6 months	2 6 44	3 45	88	1 27	7,750	Present	0 55			
37	M 51	49	Diarrhoea and loss of weight for 2 years	10 10 42	2 5	70	1 4	9,050	Absent	Zero	28 36 5	103 136	34 20
38	M 54	41	Loss of weight and loose stools for 10 weeks	11 4 44	3 13	80	1 27	2,700	Absent				
39	M 43	13	Diarrhoea for 6 months	4 1 43	4 54	98	1 09	11,250	Absent				
40	M 31	5	Weakness and diarrhoea for 4 years	14 1 43	3 65	92	1 27	9,500	Present	1 1	43	137	27
41	F 70	65	Attacks of diarrhoea for 5 years and loss of weight for 8 months	3 9 43	3 25	90	1 38	4,800	Present	0 2	41	112	29 6
				10 9 43	3 12	84	0 96	11,550	Present	Zero			
				14 1 41	4 36	84	1 31	5,300	Present	Zero			
				13 3 44	3 8	100	1 34						
				16 9 44	3 35	90							

* Indicates absence of free hydrochloric acid after histamine

Haemoglobin scale (Haldane), 100 per cent = 13.8 gm per 100 c.c.

c mm In 10 patients there was a neutropenia (below 3,000 per c mm) and in nine a lymphopenia (below 1,500 per c mm) The white-cell counts were between 4,000 and 8,000 per c mm in 26 cases, six of which showed neutropenia and eight lymphopenia In 13 out of 17 of the cases reported by Hotz and Rohr (1938) the leucocyte counts were below 4,000 per c mm Daily reticulocyte counts on patients receiving only dietetic therapy were not greater than 2 per cent and usually less than 1 per cent, irrespective of the red-cell levels Hotz and Rohr (1938) found reticulocyte counts up to 4.7 per cent and considered such findings significantly different from those in pernicious anaemia Siderocyte counts (Grüneberg, 1941, Case, 1943, 1944) were done on 14 patients, varying from 1 to 5 per cent (normal 0.4 to 2 per cent). Stained films showed no quantitative abnormality in the thrombocytes

The initial examination of the blood-films showed two main groups In the first, the erythrocytes were well stained and presented a macrocytic picture resembling that seen in pernicious anaemia, the only differential points being the relative lack of poikilocytosis and the presence of target cells (Barrett, 1938) Though all cases showing megaloblastic erythropoiesis had this peripheral picture, there was no constant correlation between the peripheral picture and type of erythropoiesis In the second and larger group, the red corpuscles showed considerable variation in depth of staining, with marked anisocytosis and moderate poikilocytosis On the whole, the smaller cells showed hypochromia, whereas the larger erythrocytes were often normochromic and macrocytic In some cases a colour index of less than unity was noted in association with a mean cell diameter greater than 7.8μ Target cells were present in most cases in this group, irrespective of the erythrocyte levels This particular picture has been admirably described by Vaughan (1936) and the term dimorphic (Trowell, 1943) seems applicable, at least to the morphological appearances We have encountered only two patients in whom the peripheral blood appeared wholly hypochromic In Case 3 (Table IVa) examination of the Price-Jones curve showed 0.8 per cent microcytosis and a mean cell diameter of 7.1μ The mean corpuscular haemoglobin concentration was 19.2 per cent This patient was a strict vegetarian, subsequent treatment with iron, and later yeast, produced the 'dimorphic picture' and an improvement of the mean corpuscular haemoglobin concentration to 30.5 per cent Similarly, there was no microcytosis and little response to iron therapy in Case 43 (Table IVa) who had a mean corpuscular diameter of 7.35μ and a mean corpuscular haemoglobin concentration of 25.9 per cent An erythroblastic type of anaemia (Bennett, Hunter, and Vaughan, 1932, Mackie, 1933, Hotz and Rohr, 1938, Snell, 1939, Frostad, 1939) was not encountered in any of our cases

Determination of the packed cell volume, mean cell volume, and mean corpuscular haemoglobin concentration were made by Wintrobe's (1931) technique The mean cell diameters were calculated from photographs of cells projected at 2,000 magnification from dry films stained with eosin In 21 patients with varying degrees of anaemia (Table IVa) these values ranged from 7.1 to 9.25μ (mean 8.4μ) with an average standard deviation of 0.796 (range

TABLE I VA

Haematological Findings in 21 Patients, Determinations in most Cases shortly after the Initial Examination

Case	Date	Red cells per (millions) c mm	Haemoglobin (%)	Colour index	Mean corpus- cular volume (c μ)	Mean corpus- cular haemo- cular con- centration (%)	Packed cell volume (%)	Mean corpus- cular di- ameter (μ)	ρ	Microcytosis (%)	Microcytosis (%)	Cell thickness (μ)	Diameter thickness ratio
1	5 6 14	4 69	56	0 6	70 36	23 33	33	7 95	1 01	21 4	2 8	1 42	5 6
2	22 3 41	3 39	32	0 49	67 8	19 2	23	7 12	0 762	0 6	0 8	1 7	4 10
3	8 1 46	4 34	86	0 99	89 8	30 5	39	7 81	0 558	7 2	0	1 82	4 32
4	20 4 14	3 34	81	1 27	80 5	30 3	31	8 10	0 96	20 4	0 08		
5	26 1 46	3 85	65	0 88				7 52	0 745	4 8	0	1 83	4 11
6	23 11 43	1 82	53	1 4	125	30 4	24	9 05	0 917	0 0	0	1 91	1 72
7	15 3 16	3 10	82	1 28	137 9	25 73	44	8 18	0 605	24	0	2 52	3 23
8	17 1 14	2 3	66	1 43	132 6	29 8	30 5	9 18	0 898	68 2	0	2	4 50
9	25 5 16	2 92	68	1 17	106 1	30 29	31	7 83	0 5	3 7	0	2 2	3 56
10	17 1 44	2 66	68	0 99	114	30 8	30 5	9 02	0 89	94 4	0	1 78	5 00
11	27 4 6	4 02	80	0 99	97	28 32	30	7 25	0 465	Zero	0	2 33	3 07
12	13 2 45	1 22	36	1 5	135 1	34 7	16 5	9 25	1 04	93 2	0	2 05	4 51
13	16 3 16	3 14	86	1 25	120 6	28 0	11 5	8 00	0 74	81 1	0	1 02	4 00
14	28 0 12	3 59	90	1 25				8 48	1 18	13 12	1 8		4 03
15	30 1 46	4 5	70	0 78	80	26 9	36	7 68	0 65	8 49	4 2	1 92	1 5
16	12 6 46	4 09	94	0 94	88 1	29 2	44	7 96	0 635	20 6	0	1 77	
17	27 2 11	2 21	58	1 31				8 16	0 799	34	0		
18	4 1 16	5 15	102	1 01				8 06	0 56	30 2	0		
19	11 10 15	3 14	54	0 85				9 04	0 905	10	0		
20	8 3 46	3 73	70	0 91	91 1	28 4	34	8 16	0 818	10 1	0	1 74	4 75
21	27 2 15	3 35	80	1 2	106 3	29	40	8 33	0 682	8 21	0 04	1 95	4 28
22	27 1 15	3 85	60	0 78	90 9	23 7	35	8 18	0 752	9 2	0 04	1 73	4 7
23	13 9 45	2 66	74	1 4	124	20	35	8 55	0 71	73 6	0	2 02	4 38
24	10 5 46	1 56	78	0 87	78 9	20 9	36	7 57	0 69	9 2	1 12	1 65	4 6
25	5 4 15	1 01	46	1 21				8 68	0 88	10 12	0		
26	2 6 14	3 45	88	1 27	103 7	28	34	9 08	0 805	73 5	0 04	1 8	4 75
27	12 4 43	2 7	70	1 13	75 4	25 9	25	8 55	0 857	65 2	0 4	1 6	4 6
28	7 9 46	3 38	18	0 7				7 37	0 81	0 08	0 08		

TABLE IV B

Haematological Findings in Four Patients with Numerically Normal Blood Counts Cases 13 and 15 are also included in Table IV A

Case	Date	Red cells per (millions) c mm	Haemoglobin (%)	Colour index	Mean corpus- cular volume (c μ)	Mean corpus- cular haemo- cular con- centration (%)	Packed cell volume (%)	Mean corpus- cular di- ameter (μ)	ρ	Microcytosis (%)	Microcytosis (%)	Cell thickness (μ)	Diameter thickness ratio
9	30 4 16	4 60	92	0 98	95 9	28 2	15	7 36	0 608	8 26	0 08	2 32	3 17
13	12 6 16	4 99	94	0 94	88 1	29 2	44	7 96	0 635	7 98	0	1 77	4 5
15	4 1 46	5 15	102	1 01				8 06	0 56	6 82	30 2		
16	24 5 16	4 45	92	1 05	98 9	28 2	15	7 37	0 541	7 35	0	2 32	3 18

0.46 to 1.18) and average coefficient of variation 9.64 per cent (range 6.4 to 13.12). In the whole series, the mean corpuscular volume varied from 67.8 to 135 c μ and the mean corpuscular haemoglobin concentration from 19.2 to 34 per cent. Although the expected correlation between the cell volume and cell diameter was usually obtained, some cases failed to show a significant increase in volume in the presence of a measured increase in diameter. This may possibly be explained by the finding of abnormal diameter thickness ratios and thinner cells. According to Price-Jones, Vaughan, and Goddard (1935) and Haden (1934), the mean cell thickness is normally between 1.73 and 2.55 μ , and the diameter thickness ratio from 2.4 to 4.2. In our series, 22 estimations of the mean corpuscular thickness varied between 1.42 and 2.52 μ , but only seven exceeded 2 μ , and in 15 cases the diameter thickness ratio was greater than 4.2. Calculations based on figures published by Vaughan and Goddard (1934) in a case of idiopathic steatorrhoea show a similar increase in the diameter thickness ratio.

A change from a hyperchromic to hypochromic anaemia and *vice versa* in terms of colour index has been described by many workers, but we have found that this may not be associated with any marked change in mean cell diameter. As can be seen from Table IVA and from curves published by Bennett, Hunter, and Vaughan (1932) and Mogensen (1938), a low colour index may be associated with a considerably raised mean corpuscular diameter. In five of our cases, the transition did not appear to be related to the onset of a remission, or to the development of iron-deficiency, the mean corpuscular haemoglobin concentration showing very little change (e.g. Case 4, Table IVA).

Fragility Fragility tests, carried out by a modified Creed's (1938) method, were performed upon 18 patients. With one exception (Case 16), the cells showed an increased resistance to haemolysis by hypotonic saline solution which was independent of the degree of anaemia. No difference in the results, in three cases, was detected when the washed cells of the patient were reconstituted with normal lipaemic serum. As opposed to the findings in steatorrhoea, fragility tests in six treated pernicious anaemia patients, with normal blood counts, showed no abnormality.

Sternal puncture Sternal punctures were carried out on 17 cases, using Salah's (1934) needle and aspirating not more than 0.25 c.c. of material. The sternal marrow films were stained by the Jenner-Giemsa stain and in every case showed erythroblastic hyperplasia. The film appearances showed two types of marrow reaction (Table V). The first type (4 cases, Plate 1, Fig. 1) was hypercellular, megaloblastic, and indistinguishable from that seen in pernicious anaemia in relapse. The peripheral blood had the macrocytic picture described above and tended to low values of red cells and haemoglobin. Similar bone-marrow findings have been reported by Rohr (1936), Hotz and Rohr (1938), and Scott (1939). The second type (Plate 1, Fig. 2) showed erythroblastic hyperplasia in which there was a variable mixture of deformed iron-deficiency normoblasts and atypical erythroblasts of large size. The latter cells showed premature haemoglobinization and were intermediate in size between typical normoblasts

TABLE V

Sternal Puncture Findings

[illegible]

and megaloblasts at the same stage of ripening of the cytoplasm. Late polychromatic and eosinophilic erythroblasts of this type still showed some reticular staining of the nucleus, though usually much less than in the comparable megaloblast of pernicious anaemia. Since complete nuclear pyknosis was rarely seen, differentiation of the late forms of these cells from orthochromic megaloblasts was sometimes extremely difficult. At the polychromatic stage, however, the nuclear chromatin did not show the characteristic open network arrangement of the megaloblast of Ehrlich and Lazarus (1898). We have, therefore, regarded these cells as atypical normoblasts of large size. Although the iron-deficiency normoblasts appeared identical to those seen in idiopathic hypochromic anaemia (Stodtmeister, 1937, Scott, 1939), there were two non-morphological points of difference. The Price-Jones curves in the peripheral blood did not show microcytosis and the normal response to iron therapy was not seen. In many smears, the large normoblasts could be traced from the basophilic to the orthochromic form and we considered that they were the probable precursors of the macrocytes seen in the peripheral blood, whereas when the iron-deficiency normoblasts predominated, the Price-Jones curves fell within normal limits. Leucopoiesis showed no constant changes, though very occasionally giant metamyelocytes and band forms were seen.

Serum-bilirubin The serum-bilirubin exceeded 0.5 mg per 100 c.c. in eight cases, the highest being 1.95 mg per 100 c.c. Such values, though in some cases within the normal range, fell to less than 0.5 mg per 100 c.c. with subsequent clinical and haematological improvement. These findings are similar to those noted without exception by other workers.

Pigment excretion Determinations of the faecal and urinary pigment excretion were carried out in 11 patients on a 50-gm. fat diet (Table VI). The method used is based on the spectrometric estimation of zinc salt for total bile pigment and Ehrlich's diazo reaction for urobilin described by Elman and McMaster (1925), Watson (1937), Baar and Hickmans (1941), and Heilmeyer (1943).

Gastric acidity Free hydrochloric acid was present in the gastric contents of 31 patients, in 11 it was absent, five of these after histamine injection. In three cases test-meals were not carried out. Free hydrochloric acid was present in 63 out of the 106 cases collectively recorded by Witts (1932), Bennett, Hunter, and Vaughan (1932), Thaysen (1932, 1935), Moore, O'Farrell, Geraghty, Hayden, and Moriarty (1936), Hotz and Rohr (1938), and Snell (1939).

Other laboratory data Serum-cholesterol levels were estimated in 34 fasting patients. Values below 100 mg per 100 c.c. were found in 15, between 100 and 150 mg in 10, between 150 and 200 mg in seven, and between 200 and 300 mg in two patients. In 19 of these patients, free and ester cholesterol were also estimated, in 12, the ratio of free to total cholesterol was significantly increased, the normal being 0.24 to 0.32 (Peters and Man, 1943). Similar results were noted in non-fasting patients. The serum-cholesterol did not invariably return to normal with improvement in the patient's condition and blood count. The serum-proteins were estimated upon 55 occasions in 37 patients. In only two patients were the total proteins below 5 gm per 100 c.c., eight were between

5 and 6 gm, 18 between 6 and 7 gm, three between 7 and 8 gm, and six between 8 and 9 gm per 100 cc Cephalin flocculation (Hanger, 1939), colloidal gold (Gray, 1940), and thymol turbidity (MacLagan, 1944) tests were performed on 21 patients, with abnormal findings in one or all the tests in 10 cases. No significant difference, clinically or haematologically, could be demonstrated in these patients.

Response to therapy As a means of investigating the aetiology of these anaemias, the haematological responses to purified and crude liver extracts,

TABLE VI
*Daily Pigment Excretion per 100 gm of Circulating Haemoglobin on
50 gm Fat Intake*

Case	Haemo- globin (%)	Urobilinogen mg per 100 gm of circulating haemoglobin in 24 hrs	Stercobilinogen mg per 100 gm of circulating haemoglobin in 24 hrs	Total bile pig- ments in urine per 100 gm of circulating haemoglobin in 24 hrs	Total bile pig- ments in faeces, per 100 gm of circulating haemoglobin in 24 hrs
7	78		9.7		78
11	80	0.58	3.1	47.5	105
13	76		11.2		190
15	94	0.23	2.8	42.5	123
	94*	0.29	5.7	91.5	212
	94†	0.27	4.05	66.5	254
22	72	0.56	5.95	47.3	158
	70	0.5	5.0	58.0	147
	72	0.39	7.6	54.6	119
23	84	0.11	4.0	20.7	59
34	80	0.23	6.5	51.8	101.5
37	80		17.0		193
	80		7.4		64.7
43	50	0.11	0.965	41.0	33.1
44	42	0.215	6.1	34.8	214
45	100	0.06	1.56	54.0	136

11 normal controls

Range	0.068 to 0.6	0.62 to 6.9	10.7 to 54.7	30.9 to 125
Average	0.182	2.54	30.6	79.4

* 72 gm fat intake—predominantly unsaturated fats

† 72 gm fat intake—saturated fats

vitamins, amino-acids, and iron have been studied.² Assessment of results, however, in a chronic disorder subject to relapses and remissions apparently spontaneous in origin is difficult. Nevertheless, in spite of using massive doses of the substances concerned, it proved difficult to restore the red cell and haemoglobin levels to normal. In only six cases was this result attained. Further detailed examination of five of these patients showed persistent abnormalities of the erythron, increased mean cell volume, increased mean cell diameter, or increased resistance to hypotonic saline. In the sixth case the blood was normal. In all six patients, however, the underlying fat absorption defect

² Anahaemin, Examen, Examen filtrate, Plexan (= Examen + Examen filtrate), vitamin B complex (Lederle), Hepaglandol, Oxoid, Hepalon, Livadex, Parke Davis crude liver extract, lipoid liver extract (B D H), proteolysed liver extract (Livas), oral liver extract (B P C), nicotinic acid, riboflavin, pyridoxine, dried brewers' yeast, methionine, betaine, parenteral yeast (Glaxo), choline, and iron.

was still present. The response to liver therapy was variable and in none was it comparable to that seen in pernicious anaemia. Purified liver fractions of known potency (*Anabaemin*, *Examen*) were administered to 11 patients, in doses of 6 to 24 c.c. within a week, with little effect on the red cell count or reticulocytes. Crude liver extracts, as exemplified by *Plexan*, produced both symptomatic and haematological improvement, but in such cases improvement was slow and incomplete, and abnormal erythroblasts persisted in the bone-marrow. In our series, the aetiological role of iron-deficiency as a major factor in the hypochromic anaemias encountered could not be confirmed, though the finding of some reduction in mean corpuscular haemoglobin concentration was frequent and has usually been accepted as evidence of such a deficiency. Ferrous sulphate (gr. 18 daily) was given prior to other therapy to four patients (Cases 3, 11, 21, and 22) with a hypochromic blood picture. In Case 11, a good response was noted and a normal blood count obtained, but later it could not be maintained either by iron or various liver preparations. In Case 3, a vegetarian patient, iron at first caused an improvement, but later the addition of yeast appeared necessary to maintain improvement. Cases 21 and 22 showed no response. In 12 other patients, only slight improvement in the mean corpuscular haemoglobin concentration was seen and in no case was it possible to restore and maintain normal blood values by iron administration alone. Furthermore, Price-Jones curves in those cases examined did not reveal the microcytic component usually associated with an iron-deficiency anaemia.

Fatal cases. Few reports are available of the post-mortem findings of the bone-marrow in idiopathic steatorrhoea. Gloor (1930) reported slight hyperplasia in spite of the picture of a non-regenerative anaemia in the peripheral blood. Starr and Gardiner (1930) and Hansen and Staa (1936) also noted slight hyperplasia, though Turnbull (1936) did not find any abnormality in a man aged 56 years whose blood was normal during life. Hotz and Rohr (1938) reported three cases showing hyperplasia, but, of the three, only one appears to have been truly idiopathic in origin. Witts (1932) and Piney (1942) both stated that aplasia of the bone-marrow may be found, but did not give any substantiating details. Seven of our cases have died (Table III). Autopsies were made on four patients (Cases 35, 38, 39, and 40). Case 36 died in congestive heart failure with active rheumatic heart disease. The other two patients died at home three and five months after their last attendance at hospital, when their blood counts were satisfactory. Five patients (Cases 35, 36, 38, 39, and 40) maintained adequate blood counts and in none could it be stated that anaemia was more than a small contributing factor in their deaths. Examination of the bone-marrow of the femur in three cases (Cases 35, 38, and 40) showed a moderate degree of hyperplasia, whilst the fourth case (Case 39) showed an essentially normal picture. In none was there any evidence of aplasia.

Discussion

Many hypotheses concerning the anaemia found in idiopathic steatorrhoea have been based upon the unitarian theory of the aetiology of the macrocytic

anaemias (Castle, 1929, Strauss and Castle, 1932, Castle and Ham, 1936) The similarities, however, between the macrocytic anaemias of steatorrhoea and pernicious anaemia are superficial, and a close relationship between them could not be established in our series. Although minor differences may be seen in the morphology of the peripheral blood and in the Price-Jones curves, more significant differences are the high incidence of free hydrochloric acid in the gastric contents and the demonstration of intrinsic factor in the gastric juice of one of our patients. Furthermore, refined liver extracts, as prepared by the Dakin-West method of fractionation, did not produce a reticulocyte response or any dramatic change in the blood picture in our patients, even in those presenting sternal marrow findings identical to those in pernicious anaemia. In describing our bone-marrow findings, the term megaloblast has been strictly reserved for the type of cell seen in pernicious anaemia in relapse, since cells of this kind are familiar to all haematologists and thereby confusion may be avoided. The large normoblasts which we have described appear to be similar to those recorded in nutritional macrocytic anaemia by Trowell (1943) as nutritional anaemia megaloblasts, and by Farley, Bromfield, Foy, and Kondi (1938) as megaloblasts with atypical features. They present many similarities in morphology to the intermediate normoblasts described by Israëls (1941), the large normoblasts associated with cirrhosis of the liver or uraemia (Schartum-Hansen 1937, Zanaty, 1937) and the cells described in the macrocytic anaemia associated with hepatic dysfunction (Naegeli, 1931, Rossier, 1932, Schulten, 1937). In the majority of our cases, therefore, we have considered the circulating macrocytes to be associated with an atypical normoblastic erythropoiesis, though in a small minority erythropoiesis may be dysplastic and morphologically indistinguishable from pernicious anaemia. To sum up, in spite of some superficial similarities, there appears to be ample evidence that the macrocytic anaemia of idiopathic steatorrhoea has a different aetiology from pernicious anaemia and that lack of haemopoietin plays little part.

Iron has been assigned a primary aetiological role in the hypochromic anaemias (Bennett, Hunter, and Vaughan, 1932, Hotz and Rohr, 1938, Hawes, 1942). In our hands, however, iron has given equivocal results. Minor degrees of iron-deficiency were remedied in some cases, but the finding of a low colour index or low mean corpuscular haemoglobin concentration was not an indication that such blood pictures could be corrected by the administration of iron alone. Some factor other than the simple administration of iron appeared to be necessary for the normal haemoglobinization of the red cells in such patients.

A consistent feature in our series has been decreased fragility of red cells to hypotonic saline, similar to that noted in a number of anaemias (Dacie and Vaughan, 1938), nutritional macrocytic anaemia (Wills and Evans, 1938), and thalassaemia (Valentine and Neel, 1945). Barrett (1938) associated this finding with the presence of target cells. Valentine and Neel (1944) suggested that these cells were the result of altered environment, since they were able to produce them by suspending normal erythrocytes in plasma or serum rendered hypertonic by the addition of chemicals or evaporation. Bohrod (1941) has pointed

out that target cells occur in a number of conditions associated with blood-loss, irrespective of its cause, and considered that this type of erythrocyte was a young cell, comparable in many ways to the reticulocyte, and that it was produced by the bone-marrow in response to excessive blood-loss from any cause. Target cells in our series occurred independently of the presence of anaemia, and the occurrence at normal red cell levels of both decreased fragility and target cells suggests the existence of a defect which is independent of, and precedes, the anaemia. There is no evidence as yet with regard to factors in the plasma influencing the red cell membrane, and thus decreased fragility *in vitro* cannot be related to specific conditions in the body.

The rapid fall in red cells and haemoglobin that may occasionally be noted suggests a haemolytic process, at least comparable to that which has been demonstrated in pernicious anaemia (Watson, 1937), and the finding of increased erythropoiesis in the bone-marrow with relatively static peripheral blood counts might be interpreted as the effect of increased red cell destruction. Such cellularity might also be regarded as evidence of a maturation defect. The usually accepted criteria of increased red cell destruction, bilirubinaemia, raised reticulocyte count, and increased pigment excretion have been investigated in our cases. Serum-bilirubin levels have not been markedly abnormal. In Case 5, a relatively rapid fall of red cell and haemoglobin values was associated with a rise of bilirubin. In the few cases in which increased bilirubin values were noted when first seen, the counts were relatively low, and may, of course, have followed a similar rapid decrease in red cells. Abnormal urobilinuria, as noted by Vaughan (1936), occurred only occasionally. Reticulocytosis prior to therapy was not present, even at low red cell levels. Total pigment excretion in the urine and faeces was within normal limits, but when the outputs in faeces and urine are considered separately, there are differences, possibly significant. In five patients out of 11, the faecal pigment excretion was above normal, but where the suspected degree of haemolysis is only slight, several estimations must be made for accurate assessment. These findings are similar to those noted by Bomford and Rhoads (1941) in 15 out of 30 cases of refractory anaemia, in some of which it was considered that dysfunction might explain the findings. Liver-function tests were abnormal in some of our patients who showed an increased output of pigment, but the difficulties of interpreting such tests need not be stressed, and the role of the liver in refractory anaemias must, at present, remain obscure. There is, therefore, little reliable evidence of increased red cell destruction in idiopathic steatorrhoea. The finding of some increased faecal pigment excretion in a condition with abnormal fat absorption focuses attention on the work of Josephs, Holt, Tidwell, and Kaye (1938, 1942) and Johnson, Freeman, and Longini (1944). The former workers showed that increased faecal pigment excretion in normal infants may be directly related to an increase in fat intake. The latter, as a result of a long series of experiments, suggested that fat ingestion contributes materially to the daily destruction of red cells in normal man and that it may even play some part in the aetiology of pernicious anaemia. They claim to have demonstrated haemolytic properties in the

thoracic duct lymph and related these to fatty acids and soaps that had escaped resynthesis. In animal experiments, however, it can be shown that fatty acids and soaps tend to pass with the portal rather than the systemic circulation and we could find no evidence of haemolysis in the systemic blood. It is possible that haemolysis may occur in the portal blood and so offer an explanation of the relatively high faecal:urine pigment ratio. This haemolytic factor might well be accentuated by the abnormal fat absorption of idiopathic steatorrhoea, in which 70 per cent of ingested fat appears to pass into the body by some alternative pathway (Cooke, Elkes, Frazer, Parkes, Peeney, Sammons, and Thomas, 1946).

As Bethell, Sturgis, Rundles, and Meyers (1945) pointed out, the conception that faults in fat absorption may give rise to blood disorders opens up wide fields of investigation. The lack of correlation between the haematological improvement and the fat absorption defect, and the occurrence of death with a relatively normal blood picture, both in our series and in those of other workers (Hotz and Rohr, 1938, Snell, 1939), might be considered as evidence against the anaemia being secondary to the underlying fat absorption defect. It can be shown, however, that there are aetiological differences between the various types of defect. Thus the absorptive defect persists in idiopathic steatorrhoea, whereas in tropical sprue and pellagra the defect may disappear entirely. Again, Adlersberg and Sobotka (1943) have demonstrated high vitamin A levels, and we have found normal chylomicrograph counts in cases of chronic granulomatous enteritis, in contrast to the low values in idiopathic steatorrhoea, though the quantitative fat absorption defect is similar in the two conditions. It seems, therefore, that qualitative changes in fat absorption may occur in the absence of any alteration in the total amount of fat absorbed. It is probable that such qualitative changes may occur in the phasic periods of steatorrhoea which might account for the haematological variations. Thus, if the varied haematological responses in idiopathic steatorrhoea are considered in relationship to the multiple factor hypothesis (Jacobsen and Subbarow, 1937, Subbarow and Jacobsen, 1945) and recent demonstrations of the effects of specific chemical substances, such as folic acid and thymine, it may be that the reticulocyte responses encountered have been due to the replacement of temporary deficiencies of various accessory factors which were conditioned by, or dependent on, an underlying fault which has not yet been affected by treatment.

Summary

1 In a series of 45 cases of idiopathic steatorrhoea, 33 patients had red cell counts above 2,500,000 per c mm and haemoglobin values above 50 per cent. Ten had a leucopenia and only two had a white cell count above 10,000 per c mm. Mean cell volume varied from 67.8 to 135 c μ and mean corpuscular haemoglobin concentration from 19.2 to 34 per cent. The mean cell diameter (Price-Jones method) in 21 patients varied from 7.1 to 9.25 μ (mean 8.4 μ). The diameter:thickness ratio was increased and greater than 4:2.1 in 15 of these cases. Resistance to hypotonic saline was consistently increased.

2 Stained films of peripheral blood showed two groups—a small group in which the morphological features resembled pernicious anaemia, but for the presence of target cells and a lesser degree of poikilocytosis, and a larger group which showed considerable variation in staining, marked anisocytosis, moderate poikilocytosis, and many target cells, the macrocytes on the whole being well stained and the smaller cells poorly stained

3 Sternal puncture in 17 cases showed four in which the erythropoiesis was dysplastic and indistinguishable from pernicious anaemia. The other 13 showed orthoplastic erythropoiesis with a mixture of iron-deficiency normoblasts and large atypical normoblasts, the proportion varying from case to case

4 Bilirubinaemia of slight degree was noted in eight patients. Faecal pigments were significantly increased in five out of the 11 cases examined. Free hydrochloric acid was present in the gastric contents of 31 out of 42 patients examined. The fasting serum-cholesterol was less than 100 mg per 100 c.c. in 15 patients out of 34

5 Seven patients died, autopsies being performed on four. Anaemia was not severe and did not appear to be a primary cause of death in any patient. The femoral bone-marrow showed hyperplasia in three cases and normal cellularity in the fourth

6. It was not possible to demonstrate any consistent effect on the blood picture after treatment with liver preparations, iron, vitamins, and amino-acids. Six patients attained normal red cell and haemoglobin levels, but in all evidence of steatorrhoea was still present. In five, abnormalities such as macrocytosis, increased mean corpuscular volume, decreased fragility, and target cells were still present

7 The varied response to liver preparations in our series, the lack of response to purified liver extracts, even with megaloblasts in sternal marrow films, the presence of free hydrochloric acid in the gastric contents of the majority of patients, and the demonstration of intrinsic factor in the gastric juice of one of our patients provide strong evidence that the macrocytic anaemias of steatorrhoea cannot be explained by the unitarian theory ascribed in general to macrocytic anaemias

8 The possibility that abnormalities of fat absorption may cause more rapid cell destruction, and the relationship of this underlying defect to the anaemia of idiopathic steatorrhoea are discussed

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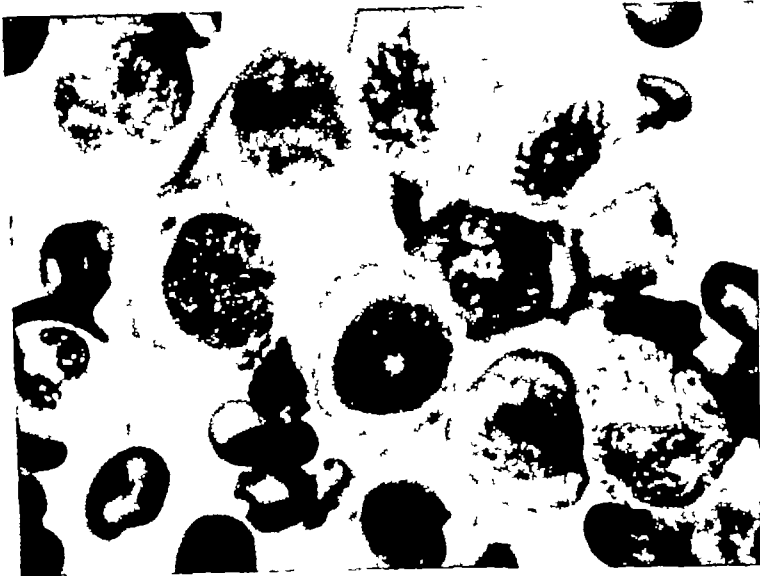


FIG 1 Smear of sternal marrow from Case 12, showing megaloblastic erythropoiesis indistinguishable from pernicious anaemia in relapse. The polychromatic megaloblast on the left of the group shows the typical nuclear structure of the megaloblast of Ehrlich. Peripheral blood—mean corpuscular diameter 9.25μ .



FIG 2a

FIG 2b

FIG 2c

FIG 2a Bone marrow smear from Case 1 showing a fully haemoglobinized large atypical normoblast. This cell shows a 'shift to the left' of haemoglobinization. Central erythropoiesis in this case is active, with large numbers of both atypical normoblasts and 'iron deficiency' normoblasts. The peripheral blood is hypochromic, mean corpuscular haemoglobin concentration 23.3 per cent, mean corpuscular diameter 7.95μ , diameter thickness ratio 5.6:1.

FIG 2b Bone marrow smear from Case 43, showing a group of typical 'iron deficiency' normoblasts with a small irregular rim of polychromatic cytoplasm. Erythropoiesis is almost exclusively of this type. Peripheral blood—mean corpuscular haemoglobin concentration 25.9 per cent, mean corpuscular diameter 7.37μ , diameter thickness ratio 4.6:1.

FIG 2c Stained bone marrow film from Case 42, showing a clump of atypical normoblasts. These cells are almost completely haemoglobinized, but still show considerable reticulation of the nucleus. This is the predominant type of normoblast present in the bone marrow. The peripheral blood is macrocytic, mean corpuscular diameter 8.7μ .

IDIOPATHIC PULMONARY HAEMOSIDEROSIS (ESSENTIAL BROWN INDURATION OF THE LUNGS)¹

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With Plates 2 to 4

Introduction

THE clinical features of pulmonary haemosiderosis are distinctive, and usually occur with some uniformity, so that once a case has been seen, others can be readily recognized. Yet the condition must be considered a rare one because to 1947 we have found reports of only 17 cases, all but one fatal; eight were from German sources, two American, four Scandinavian, one Australian, one Swiss, and one Italian. To these we have a further seven to add, seen in the period 1938 to 1947 at The Hospital for Sick Children. The symptomatology, results of laboratory investigations, and morbid anatomy will be described, and views on pathogenesis discussed.

With one exception, a man of 38 years, claimed by Borsos-Nachtnebel (1942) to be a case of pulmonary haemosiderosis, the condition has been diagnosed exclusively in children from a few months old to 16 years of age. The symptoms consist of recurrent attacks, often sudden in onset, of fatigue, cyanosis, and pallor, increasing dyspnoea, and acceleration of the pulse-rate. Cough is troublesome, often followed by vomiting, and at times traces or even considerable quantities of blood are noticeable in either sputum or vomit. The test for occult blood in the faeces becomes positive. Abdominal pain may be complained of, and the temperature towards the height of an attack rises either slightly or to as high as 103° F. Severe attacks can be very alarming, the patient is restless, apprehensive, and may even appear to be dying. Each attack commonly lasts from two to several days, or longer in a subacute phase, and towards its termination in the more acute type the patient, besides showing an increasing pallor, may become jaundiced. Liver dullness is increased and the spleen becomes palpable. There may be clubbing of the fingers.

The following is an account of recurrent typical attacks in a girl of 12 years, first affected at the age of two years. The attacks increased in frequency and severity up to the age of eight years, but have been less frequent since. On entering an attack, the child becomes languid and tired, the pulse-rate rapidly rises to 160 to 180 per minute, and cyanosis appears. Within 12 hours she is

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of the alveolar walls also contain haemosiderin, and many are desquamated within the alveoli, which also contain red blood-cells and haemosiderin granules lying free. Considerable thickening of the alveolar walls and interlobular and peribronchial tissues is apparent. Haemosiderin granules are contained within the interstitial tissues, and in the enlarged broncho-pulmonary and tracheo-bronchial lymphnodes. Other notable features recorded have been diffuse pulmonary fibrosis, capillary fibrosis, fragmentation and distortion of the elastic fibres in the alveolar walls, arterioles, arteries, and veins, deposits of haemosiderin from previous haemorrhages, and evidence of fresh bleedings into the alveoli.

Summary of Previously Reported Cases

Ceelen (1931), at the Berlin Pathological Society, was the first to describe autopsies on two cases of pulmonary haemosiderosis. One, a boy, aged five and a half years at the time of death, had had symptoms from 12 months of age, consisting of cough, vomiting, blood-stained sputum, and anaemia. On section, the lungs showed red-brown staining, the pulmonary lymphnodes were swollen, and there was increase in size and hypertrophy of the right side of the heart. Microscopically, there was remarkable thickening of the pulmonary interstitial tissue, with excessive masses of heart-failure cells containing large quantities of iron pigment in the alveoli. The heart-muscle appeared normal. The second child, a girl of 10 years, had one month's history of vomiting, fever, abdominal pain, severe breathlessness, marked pallor, and cyanosis. The cardiac dullness was increased transversely, the liver enlarged, and the spleen palpable. A blood examination showed red cells 2,780,000 per c mm, haemoglobin 25 per cent, white cells 10,600 per c mm, poikilocytosis, anisocytosis, and polychromasia. At the post-mortem examination, haemorrhagic pachymeningitis was found as well as chronic haemorrhagic induration of the lungs, enlargement of the bronchial, tracheal, and abdominal lymphnodes, dilatation and hypertrophy of the right side of the heart, and coarse cirrhosis of the liver. Microscopy showed thickened alveolar, interlobular, and peribronchial connective tissues, giant irritation cells, excessive alveolar content of haemosiderin-laden cells, and thickening, splitting, and fragmentation of the elastic tissue fibres of the alveolar walls. The liver showed evidence of marked venous congestion with centrilobular fatty changes, and the Malpighian bodies of the spleen were greatly enlarged. In both cases there were signs of severe disturbance of the lesser circulation. Ceelen postulated either a primary tissue defect of the lungs, or damage to the lung tissue secondary to some other disease.

Montaldo (1938) described a female infant, aged 21 months, with severe anaemia (red cells 1,600,000 per c mm and haemoglobin 22 per cent) after a feverish attack, soon followed by progressively severe attacks of dyspnoea. Slight jaundice and urobilinuria were present. The heart, spleen, and liver were clinically not enlarged. There were no physical signs in the chest, but X-rays showed diffuse multiple infiltrations in both lungs. The child died after three

seriously ill, anxious, and apprehensive, with severe dyspnoea, extreme cyanosis, and fever up to 103° F. A frank haemoptysis occurs, and cough and vomiting are troublesome. After several days of increasing pallor, she finally becomes jaundiced. The disturbance in the lesser circulation is further revealed by dilatation of the right side of the heart, which may develop a gallop-rhythm, some fulness of the veins in the neck, an enlarging liver, a palpable spleen, and a few moist sounds in the lungs.

The usual order in which symptoms appear is tachycardia and cyanosis, followed in 12 to 24 hours by dyspnoea, pallor, and fever, maximal at the height of an attack, and possibly associated with jaundice. The clinical picture is one of congestive heart failure and is suggestive of a severe disturbance of the lesser circulation. Recovery from these congestive-dyspnoeic episodes may take place quickly, but in the intervals the patients usually remain debilitated and underweight, and easily become short of breath on exertion. Owing to the obvious and often sudden onset of pallor with subsequent slight jaundice, a diagnosis of haemolytic anaemia is apt to be made, and the true nature of the condition may escape notice from want of radiographic examination of the lungs. Pulmonary physical signs between attacks are insignificant, and there may only be some scattered rhonchi over the lungs. By comparison, the X-ray appearances are often grossly abnormal. The commonest features are mottled shadows most noticeable in the hilar areas, and a diffuse speckling throughout the lung fields. These abnormal shadows become accentuated in an attack. Evidence of a partial lobar collapse is often visible. The X-ray appearances of the lungs frequently have a superficial resemblance to those of miliary tuberculosis, but, in the place of miliary dots, one can usually distinguish small, clear, circular spaces surrounded by thickened opaque walls giving a pumice-stone appearance. There is much similarity in the picture to that presented either by sarcoidosis or Gaucher's lipoidosis involving the lungs. The degree of hilar mottling attained during an attack has been likened to the root-shadows seen in cases of mitral stenosis. The cardiac shadow is enlarged chiefly towards the right, and the pulmonary conus may be prominent. Blood estimations show a severe type of secondary hypochromic anaemia, and often a high reticulocytosis.

Of the 17 reported cases, five were male, 10 female, and in two cases the sex was not stated. The age of onset of symptoms was between early infancy and middle childhood. Only one case, already referred to, was in an adult. In no instance has a family tendency been recorded. In all but one of the 17 cases the condition ended fatally, with signs of congestive failure of the lesser circulation, after one or several years of intermittent ill health. At autopsy, the main and most constant changes are to be found in the lungs. Macroscopically, the lungs appear full and firm, of a dark reddish-brown colour, with fine haemorrhages visible on the pleural surfaces. On section, there is pneumonic hepatization with a dark red-brown colour of the cut surfaces. Enlargement of the bronchopulmonary and tracheo-bronchial lymphnodes is conspicuous. The size of the heart is increased, especially on the right side. Microscopically, the alveoli in large areas are crowded with haemosiderin-laden phagocytes. Epithelial cells

age of 19 years Post-mortem examination confirmed the clinical diagnosis of haemosiderosis pulmonum

Glanzmann and Walthard (1941) described a case of idiopathic progressive brown lung induration in a girl aged 11 years, with a long history of recurrent attacks of fatigue, anorexia, dyspnoea, pallor, cough, vomit and sputum often blood-stained, abdominal pain, rapid pulse up to 180, and slight jaundice The heart was enlarged and a haemic murmur present There was severe anaemia, reticulocytosis, normal fragility, and slight eosinophilia In attacks there were a few râles in the chest, and X-rays showed in the mid-zones fine fleck-like shadows resembling the appearances associated with heart-failure At six years, the child had had scarlet fever with persistent albuminuria afterwards Her tuberculin tests were said to be negative, though her father was tuberculous and subject to haemoptysis Pathological examination showed the lungs to be large and indurated and on section dark red, and the heart and spleen were enlarged On section of the lungs most alveoli were full of erythrocytes and desquamated epithelial cells containing haemosiderin, and the swollen lymph-nodes also contained haemosiderin The alveolar walls, interstitial tissue, capillaries, and small vessels were thickened The elastic tissue was conspicuously abnormal In many alveolar walls no elastic fibres could be traced, but in apparently unaffected alveoli the elastic fibres were swollen, tortuous, and fragmented The authors spoke of a circulatory disorder of the lungs due to interalveolar cirrhosis and defective formation of the elastic fibres of the capillaries, alveolar walls, and of the interlobular septa

Borsos-Nachtnebel (1942), quoted by Scheidegger and Dreyfus (1945), recorded three cases of 'pulmonary-haemosiderotic anaemia' in a girl of two and a half, a boy of four, and a man of 38 years, the only instance of the condition being described in an adult The lungs in these cases were the only organs affected, though the right side of the heart was reported to be hypertrophied and some myocardial degeneration was present The author supported the theory of a specific structural defect of the lung tissues

Pilcher and Eitzen (1944) described a case of chronic interstitial pulmonary infiltration and haemosiderosis in a boy of six and a half years, who for 18 months had had intermittent symptoms of increased resistance to the pulmonary circulation, fatigability, weakness, pallor, breathlessness, and slight pyrexia There was clubbing of the fingers The anaemia was severe and associated terminally with enlargement of the liver and spleen, and jaundice with an icteric index of 16 X-rays showed mottled shadows chiefly at the roots of the lungs, and enlargement of the pulmonary conus There was no blood-stained sputum noticed in this case At autopsy, the pulmonary, broncho-pulmonary, and tracheo-bronchial lymphnodes were much enlarged On section of the lungs, areas of alveoli were seen to be filled with red blood-cells and with phagocytic cells laden with haemosiderin The alveolar walls and interstitial and perivascular tissues were diffusely thickened, multinuclear giant cells were numerous among siderotic nodules, and the elastic tissue of the alveoli, arteries, and arterioles was thickened, frayed, and fragmented The principal changes were

months' illness. At the post-mortem examination, bilateral pulmonary haemosiderosis was found. The right side of the heart was hypertrophied and moderately dilated. The liver and spleen were not enlarged. The author called his case a haemolytic anaemia with pulmonary haemosiderosis.

Anspach's (1939) case was in a girl, who died aged seven years, with a history of three years' duration. The symptoms were characteristic, namely, pallor, dyspnoea, spitting of blood, moderate pyrexia of 99° to 100° F, a secondary anaemia of 2,000,000 red cells per c mm, diffuse clouding about both hilar areas shown by X-rays, and enlargement of the liver and spleen. The Mantoux reaction was mentioned as positive. In the histology, Anspach spoke of widespread deposits of haemosiderin in the pulmonary tissues, diffuse pulmonary haemorrhages, diffuse fibrosis, and a necrotizing arteritis.

Waldenström (1940, 1944) described two cases clinically. The pathology of one case was discussed by Gellerstedt (1939) and of the other by Belfrage (1943). The case of Gellerstedt (1939) and Waldenström (1940) was a boy with onset of symptoms at 13 and death at 15 years. In attacks he had cyanosis, pallor, tachycardia, dyspnoea, cough, and blood-stained sputum. The spleen was palpable. The red cells fell to 2,110,000 per c mm, with platelets 368,000 per cmm, and reticulocytes 1.8 per cent. The blood-pressure was 110/65. There were no physical signs on examination of the lungs, but X-rays showed hilar broadening and diffuse granular infiltration of the lungs, especially at the bases. On post-mortem examination, the lungs felt hardened and the cut surfaces were of a dark red-brown colour. The heart was enlarged, showing some right-sided hypertrophy and slight myocardial changes. Microscopy showed areas of alveoli packed with haemosiderin-containing epithelial cells and free red blood-cells. The walls of the alveoli, capillaries, and small blood-vessels were thickened, and the elastic tissue fibrils were in some places thickened, in others fragmented. Blood pigment was also present in the cylindrical epithelium of the smaller bronchi. Gellerstedt (1939) found the morbid changes much less developed in the heart than in the lungs, in which he thought the primary cause was to be sought. Thus he considered to be principally a local pulmonary capillary weakness, with secondary anaemia from the bleeding in the lesser circulation. The case of Belfrage (1943) and Waldenström (1944) was a girl who at 16 years of age showed signs of anaemia resembling chlorosis (low colour-index, low serum-iron, and good effect of iron therapy), but exhibited also signs of haemolysis (increased bilirubin of the blood, urobilinuria) and hyper-regeneration (reticulocytosis and possibly thrombocytosis). Slight fever and a persistent cough were noted. The lungs showed no abnormal physical signs, but on X-ray examination diffuse opacities were present on both sides. Later several attacks developed with abdominal pain, increasing dyspnoea, and anaemia accompanied by slight haemoptyses. There was severe anaemia (red cells 2,300,000 per c mm and haemoglobin 40 per cent), a normal leucocyte count (8,400 per c mm with 1 per cent eosinophils), reticulocytosis (7.7 per cent), normal red cell fragility, and a positive von Pirquet test. The blood-pressure was 130/80. The liver and spleen were not palpable. Death occurred during an attack at the

and right middle lobe, fine haemorrhages in the pleura, and enlargement of the bronchial and tracheal lymphnodes. The liver was large, the spleen slightly enlarged, and the kidneys showed fine cortical haemorrhages. On microscopy, the lungs showed oedema and desquamation of the alveolar epithelium. Some alveoli were packed with haemosiderin-laden epithelial cells, and signs of frank haemorrhage were visible. Similar haemosiderin deposits were present in the bronchial epithelium and vascular endothelium. The vessels were said to be broadened with fine fatty changes in the walls, but alterations in the elastic tissue of the vessels were said to be absent. Slight degenerative changes were described in the heart, liver, and kidneys. The authors considered an inflammatory process responsible for the changes found in the different organs, and held that a concept of a primary congenital defect of the lungs was unproved. In this case the absence of haemoptysis is important, but a benzidine test for occult blood in the stools is not mentioned. Especially at so young an age most upper-respiratory secretions are swallowed, though a haematemesis might have given evidence of bleeding.

Reye's (1945) case was a girl who died at the age of three years and 11 months, and had had an onset of symptoms 15 months previously. These consisted of pallor, cough, slight cyanosis, and vomiting, the vomitus at times containing blood. The red cells fell to 1,550,000 per c mm, the platelets were 560,000 per c mm, and reticulocytes 12 per cent. The liver was enlarged and the indirect van den Bergh test strongly positive. The tip of the spleen was palpable. The breath sounds became harsh and grunting, and X-rays showed consolidation of the base of the right lung and enlarged hilar shadows. Death was due to respiratory embarrassment. The lungs at autopsy were rubbery in consistency and of a reddish-brown colour. All chambers of the heart were dilated, but especially the right ventricle. The broncho-pulmonary lymphnodes were swollen. On section, almost all the alveoli were packed with red blood-cells and cells containing haemosiderin, and the walls of the alveoli and interstitial tissue showed thickening, fibrosis, and increase of elastic tissue. The capillaries and larger vessels were said to be normal.

Hanssen's (1947) case was that of a girl with onset of symptoms at six and a half years and death four years later. Repeated haemoptyses and a moderate degree of hypochromic anaemia were the features at first. Later, attacks of dyspnoea and cyanosis developed. Clubbing of the fingers and curving of the nails were present three years after the onset of the disease. The liver, spleen, and heart were clinically not enlarged. X-rays of the lungs showed diffuse dust-like infiltrations. The Mantoux test was negative. The haemoglobin fell to 30 per cent, but responded well to iron therapy. There was a constant reticulocytosis of 1 to 10 per cent, pathological urobilinuria, and raised serum-bilirubin. The white cells ranged from 5,500 to 12,000 per c mm, with 6 to 8 per cent eosinophils. Red cell fragility was normal. The bone-marrow was normal. The Wassermann reaction was negative. Sections of blood-stained sputum showed masses of haemosiderin-laden phagocytes and extracellular

given as diffuse fibrosis, capillary fibrosis, degeneration of elastic fibres of the alveolar septa, arterioles, and arteries, pigmentation, and focal haemorrhages

Selander (1944) wrote of idiopathic pulmonary haemosiderosis as the cause of death in a girl of eight years, who soon after birth had some difficulty in breathing, but by four years appeared to be in good health, though undersized. After pertussis at seven years, symptoms of respiratory disturbance reappeared intermittently, there being pallor, breathlessness, cough, vomiting, abdominal pain, slight pyrexia, and blood in the sputum on a few occasions. There was clubbing of the fingers and cyanosis, but no jaundice. The red cells fell as low as 1,800,000 per c mm, and the haemoglobin to 31 per cent. The breath sounds were diminished, and on X-ray examination diffuse, fine, granular mottling and increased hilar shadows in both lungs were conspicuous. The radiographic pulmonary changes waxed and waned. At autopsy the heart was enlarged, with hypertrophy of the right ventricle, and the spleen was bigger than normal. The lungs were a dark reddish-brown colour, and the hilar lymphnodes increased in size. In sections, altered and fresh blood was seen in the alveoli, as well as haemosiderin-laden cells, haemosiderin occurred in the bronchial walls, and marked thickening of the alveolar and interstitial tissues was apparent, as well as deformity and destruction of the elastic tissues, both in the vascular and alveolar substance.

Nitschke (1944) demonstrated a child to a medical society and reported also the clinical history and autopsy findings of another child. Sex and ages were not given. The common features were recurrent secondary anaemia of long standing, with only temporary response to iron therapy and transfusions, occasional haemoptyses, progressive dyspnoeic attacks, and characteristic multiple diffuse shadows in the lungs. On post-mortem examination, the lungs and regional lymphnodes were impregnated with iron pigment, but the other tissues were free from iron. The possibility of a storage disease was discussed.

Scheidegger and Dreyfus (1945) described a case of brown lung induration with secondary anaemia in a female infant of 12 months, who during life presented minimal signs. The child had been undernourished and ailing from the fourth month. At eight months, there was some cough and the hilar areas of the lungs were slightly enlarged, but the lung fields were clear, heart normal in size, dyspnoea absent, and liver and spleen not enlarged. The Mantoux reaction was negative, and the blood-sedimentation rate 3 mm after one hour. At 10 months the infant was still much underweight, with a mild cough and slight pyrexia, but no dyspnoea or haemoptysis. By X-rays and clinical examination the lungs and heart appeared normal. The blood showed a secondary anaemia, red cells 1,620,000 per c mm, haemoglobin 40 per cent, one normoblast per 100 white cells, and a blood-sedimentation rate of 40 mm after one hour. The skin was pale, but showed a brownish pigmentation. The urine contained a trace of albumen and a few red blood-cells. Numerous examinations failed to show any cardiac or pulmonary abnormalities. At 12 months the infant died suddenly. On post-mortem examination, the heart, especially the right side, was enlarged. Both lungs were of a dark red-brown colour, with induration of the lower lobes.

TABLE I
Summary of Previously Reported Cases

Case number	Author	Age at onset (years)	Age at death (years)	Haemoptysis or haematemesis	X ray pulmonary shadows	Cardiac enlargement	Palpable liver and spleen	Red cells (per c mm.)	Haemoglobin (%)	Reticulo-cytosis (%)
1	Ceelen (1931)	1	5½	+		+	0			
2	"	9½	10	Vomiting		+	0	2,780,000	25	
3	Montaldo (1938)	1½	2	0	+	0	0	1,000,000	22	
4	Anspach (1939)	4	7	+	+	0	+	2,000,000	28	
5	Waldenström (1940) and Gellerstedt (1939)	13	15	+	+	+	+	2,110,000	32	18
6	Waldenström (1944) and Belfrage (1943)	16	19	+	+	0	0	2,300,000	40	77
7	Glanzmann and Waltherd (1941)	Early childhood	11	+	+	+	0	2,647,000	20	33 to 61
8	Borsov Nachtnobel		2½				0			
9	" (1942)		4							
10	"		38							
11	Pfecher and Eitzen (1944)	5	6½	0	+	+	+	1,880,000		
12	Selander (1944)	Early infancy	8	+	+	+	0	1,800,000	31	
13	Nitschko (1944)		Childhood	+	+			Anaemia		
14	"		1	+	+	+	0	Anaemia		
15	Scheidegger and Dreyfus (1945)	1½		0	+	+	0	1,620,000	40	
16	Reyo (1945)	2½	3½	+	+	+	+	1,500,000		12
17	Hanssen (1947)	6½	10½	+	+	0	+		30	1 to 10

increasing dyspnoea and cyanosis, but there was no anaemia. Owing to war-time conditions no post-mortem was performed. Apart from recurrent haemoptyses, hypochromic and haemolytic anaemia, and milary infiltrations in the lungs, in a female child, the diagnosis was made on the demonstration of heart-failure cells in the sputum in the absence of other signs of heart disease.

Discussion of cases previously reported Table I provides details from the records of the cases previously described. Where visible bleeding, as haemoptysis or haematemesis, was absent during active phases of the disease, vomiting is sometimes mentioned. Only in Gellerstedt's (1939) case is the benzidine test for occult blood in the stools mentioned as having been done, and it was reported as positive. Radiographic changes in the lung fields, when looked for, were present in all cases. Increased praecordial dullness, usually from right-sided cardiac enlargement, was recognized in nearly all cases during life and in all cases at autopsy. In the more recent records, prominence of the pulmonary conus shown by radiography is mentioned. The liver and spleen on palpation were not invariably enlarged, though increased size might be discovered on post-mortem examination. The details of blood examinations are given in reference to active stages of the disease. Replacement of red cells to almost normal figures, especially when aided by iron therapy, took place in periods of remission. Similarly, the density of the lung shadows, hilar and parenchymal mottling, varied greatly between active and quiescent phases of the disease, being closely associated with the intrapulmonary bleeding and formation of haemosiderin deposits. In chronic cases, even in a state of prolonged remission, the pulmonary radiographic signs are almost always conspicuous, though ordinary clinical examination of the lungs may detect no abnormal signs. Figures for the leucocytes, platelets, and red cell fragility, when mentioned, were on an average normal. The blood-sedimentation rate, when mentioned, was variable, but more often within normal limits than raised. There was no indication of hypertension, the blood-pressure was 110/70 in Waldenström (1940) and Gellerstedt's (1939) case, 130/80 in Waldenström (1944) and Belfrage's (1943) case, and 120/80 in Glanzmann and Walthard's (1941) case. In these 17 cases the only extrapulmonary pathological changes more or less constantly found were cardiac dilatation, mainly right-sided, with some hypertrophy, and often some degree of hepatosplenomegaly, all of which can be regarded as consequences of progressive failure of the lesser circulation. Ceelen (1931), Gellerstedt (1939), Glanzmann and Walthard (1941), and Scheidegger and Dreyfus (1945) each described minor myocardial lesions, either microscopic foci of subchronic myocarditis, or fine fatty changes, but not degenerative changes of the elastic tissue of the capillaries as found in the lungs. A haemorrhagic pachymeningitis is mentioned in Ceelen's second case, a small retinal haemorrhage was observed temporarily in Pilcher and Eitzen's (1944) case. Scheidegger and Dreyfus mentioned some albuminuria and microscopic haematuria in their case following scarlet fever at six years. There is no evidence from the records of a familial predisposition of pulmonary haemosiderosis. In Glanzmann and Walthard's case, the child had a negative Mantoux test, though

skin The attacks subside in three or four days, and between them the child seems fairly well, although she is disinclined to play with other children, easily becoming breathless on exertion Examined in 1938, the heart was found to be a little dilated, and there was a systolic bruit at the apex This was probably attributable to her degree of anaemia, the haemoglobin being 42 per cent Two years later her attacks had increased in frequency to once every month, although their characteristics remained unaltered The blood-pressure was 115/70 Several attacks have been observed The temperature is raised to about 101° F, and moist sounds can be heard over the lungs The breathlessness and cyanosis are sufficiently alarming to demand the use of an oxygen tent, which brings considerable relief During the crises of anaemia the red cells fall to 3,000,000 per c mm or less, and the haemoglobin to 40 or 50 per cent, while the reticulocytes have risen to 22 per cent Blood regeneration occurs between attacks, with corresponding improvement in the blood counts The jaundice is of slight degree, and haemolytic in type, the van den Bergh indirect test rising to 7.5 units of bilirubin per 100 c c Since the age of seven years, small haemoptyses have occurred in some, but not in all, of her attacks A large haemoptysis took place during an attack in March 1946, together with more than the customary degree of jaundice A satisfactory recovery was made from this attack Since 1943, the heart signs have been normal The spleen has varied from being just palpable to two fingers' breadth below the costal margin The child was last examined in March 1947, aged 13 years, and was still having attacks, and easily became breathless on exertion in the intervals between attacks The following investigations were carried out

Tuberculin patch test, positive

Wassermann reaction, negative

Fragility of red blood-cells (several examinations), normal

Bleeding time and clotting time, normal

Blood-platelets, 120,000 per c mm

Sternal bone-marrow, normal

Examination of blood for methaemoglobin, methaemalbumin, and sulphaemoglobin, negative

Blood group O, Rhesus positive

Cold agglutinins were absent on one occasion, on another they were present to a titre of 1 in 8

Chest X-rays show diffuse miliary mottling over both lungs, and increase of hilar shadows comparable with those seen in congestive heart-failure

Case 2 Boy Born April 1934, died October 1938 The family history was not available At 18 months of age he had his tonsils and adenoids removed When three years of age he attended The Hospital for Sick Children on account of bilateral otorrhoea and infection of the maxillary antra After a course of treatment in the hospital he was transferred to a convalescent home because of his persistent cough The boy remained under observation at the convalescent home for 10 months During this period he had four or five attacks of fever of three or four degrees, each attack lasting two to three days and accompanied by some cyanosis and dyspnoea, together with transient impairment of the percussion note over the bases of the lungs and some accompanying moist sounds During these attacks X-ray examination showed temporary opacities at one or other lung base, and between attacks both lung fields showed opacities suggestive of unresolved pneumonia Eventually in July 1938 the child rapidly developed a severe anaemia, the haemoglobin dropping to 30 per cent This was followed in a day or so by three small haematemeses, and the boy was

the father had had haemoptyses due to pulmonary tuberculosis. In discussing the pathogenesis of pulmonary haemosiderosis, most of the authors emphasize the severe disturbance of the lesser circulation, and postulate primary retrogressive changes, or primary tissue defects, of the capillaries and interstitial pulmonary tissues, especially of the elastic tissue. As a consequence there occurs, as Anspach (1939) remarked, small or minute repeated pulmonary haemorrhages over a long period. Scheidegger and Dreyfus are alone in recording an absence of apparent changes in the elastic tissue in the lungs.

Present Material

The present series of seven cases was seen at The Hospital for Sick Children between 1938 and 1947. Five were girls and two boys, the eldest being 13 years of age at the time of writing. There was no familial incidence, and no blood-relationship discovered among the parents. The presenting clinical features may be predominantly haematological as in Case 6, and a diagnosis of severe hypochromic anaemia may be accepted until X-rays of the lungs are taken, showing the significant diffuse mottled, often milky, shadows. These, waxing and waning with the severity of the anaemic and cyanotic phases, in addition to the haemoptyses and haematemeses, indicate the true, pulmonary, source of the disease. Another unusual onset was that seen in Case 7, an infant of a few months old, with a prolonged bout of tachycardia, tachypnoea, symptoms resembling bronchitis, pallor, clubbed fingers, palpable spleen, and in the main a normal temperature. In this instance blood-stained sputum did not occur, and the benzidine test for occult blood in the stools was negative. It is often difficult to state at what age the symptoms of pulmonary haemosiderosis have commenced. A first characteristic attack may occur at any age in childhood, yet frequently a history of bronchitis and anaemia may be traced to an earlier age, often to infancy. In the present series, two patients have died and five are still living. Of the latter, the attacks up to date continue to occur in three. Only in two, young children aged five and a half and three and a half years (Cases 6 and 7), can the present state be said not to cause anxiety. Case 6 has improved in general condition, and has been free of symptoms for some time, Case 7 appears to be in excellent health. In all five living cases the X-ray appearances in the lungs are still present. Table II and Table III, presenting some of the main clinical and haematological features, are to be compared with Table I. Fuller details are supplied in the Case Reports of our own seven cases.

Case Reports

Case 1 Girl. Born 29.3.1934. The parents were healthy, and a brother born in 1939 had remained well. Previous illnesses included pertussis in 1939, varicella, epidemic parotitis, and rubella. The child was well until two years old, when she had an attack characterized by a sudden onset, with pallor, breathlessness, and slight jaundice, the whole attack abating after a week. Two years later she had pneumonia, and since then had had attacks of dyspnoea roughly every three months. These attacks take about a day to develop, beginning with restlessness and dyspnoea, and going on to pallor, slight cyanosis, and an icteric tinge to the

of the lungs became weak, and moist sounds could be heard over both lungs. Except for tachycardia, the heart seemed normal. On each occasion the state of the child seemed alarming and dangerous, and prompt resort was made to an oxygen tent. Except for the final attack, which lasted two days, each bout subsided within 12 to 24 hours, on two occasions vomiting of brownish material occurred on the day after an attack, and on the second occasion examination of the vomitus showed haemosiderin granules, some of which were intracellular. Haemosiderin was also present in a 24-hour specimen of urine. An account of the post-mortem findings is given later.

The following investigations were carried out:

Mantoux tuberculin test (1:1,000), negative

Blood-sedimentation rate, 42 mm in 1 hour

Van den Bergh direct test, negative, indirect test, 2.4 mg of bilirubin per 100 cc

Fragility of red blood-cells, on two occasions, normal.

Average daily excretion of urobilin, 0.16 mg (normal 0.5 to 2 mg)

Average daily excretion of stercobilin, 74 mg (normal 100 to 250 mg)

Blood counts were done on several occasions. The red cells varied from 3,300,000 to 5,600,000 per c mm, and the haemoglobin from 60 to 92 per cent. The white cells showed a polymorphonuclear leucocytosis after attacks, and on one occasion rose to 41,200 per c mm with polymorphonuclears reaching 90 per cent. Between attacks a count of 10,000 per c mm, of which 61 per cent were polymorphonuclear, was typical. The highest reticulocyte count was 16 per cent.

Examination of several blood-films for malarial parasites was negative.

Cold agglutinin titres of the patient's serum were:

With her own cells at 4° C, 1/10,000,000, 1/1,024, 1/64, 1/64

With Group O cells at 4° C, 1/64, —, 1/32, 1/64

With her own cells at 37° C, nil, —, nil, 1/2

With Group O cells at 37° C, nil, —, nil, 1/2

Occult blood test in stool, negative

Race-Coombs test, negative

Case 4 Girl Born 21.1939. She was an only child whose mother was Jewish and father German. The child was well until 18 months old, when she had a severe attack of bronchitis, and an X-ray of the chest at that time was said to have had the appearance of miliary tuberculosis. Since then, every few weeks the child had had feverish attacks lasting a day or two, and accompanied by an intractable cough and severe breathlessness, but without either sputum or haemoptysis. For a year and a half prior to admission to The Hospital for Sick Children, anaemia and breathlessness had become increasingly prominent symptoms, for which she had been admitted several times to hospitals, and on two occasions had been given blood transfusions. On 17.1.45, a diagnostic lung aspiration to exclude tuberculosis yielded red blood-cells and numerous pigment-filled macrophages. In September 1945 she was admitted to The Hospital for Sick Children. She was then a pale, thin child, with a slight icteric tinge to her conjunctivae, and weighed only 34 pounds. No finger clubbing was present. The throat was clean, and no abnormal signs could be made out in the heart or lungs. The tip of the spleen was palpable, the liver was of normal size, and there was no general enlargement of lymphnodes.

The following investigations were carried out:

Mantoux tuberculin test up to 1:100, negative

Chest X-ray showed a fine mottled appearance over both lungs

readmitted to The Hospital for Sick Children. By this time the haemoglobin had fallen to 16 per cent. The temperature was 104°F , there were consonating crepitations at both lung bases, and the X-ray picture was suggestive of broncho-pneumonia. Two blood transfusions totalling 650 c c were given, and a blood count two days later showed red cells 2,940,000 per c mm, haemoglobin 46 per cent, reticulocytes 11.6 per cent, white cells 11,600 per c mm, and a differential count of polymorphonuclears 81 per cent, lymphocytes 16 per cent, and monocytes 3 per cent. During the next three weeks the boy made such good progress that he was discharged, but had to be readmitted three days later on account of a return of haemoptysis and haematemesis. At this stage the blood picture was much as before except that the reticulocytes had risen to 26 per cent. The liver was noted to extend two fingers' breadth below the costal margin, and the tip of the spleen could be felt. Again under treatment the child improved, the haemoglobin rising to 64 per cent. At this stage a bronchoscopy showed both main bronchi to be of normal calibre, but there was mucopus in the right main bronchus. A bronchogram showed collapse of the right middle lobe. For six weeks the child's condition remained stationary. He was pale, but otherwise showed no symptoms. During the night of October 24, 1938, he became restless, blanched, and began coughing, the temperature rising to 99°F . Next morning he had a large haemoptysis, and although a blood transfusion was started, he died before a significant quantity of blood had been introduced. An account of the post-mortem findings is given later.

Investigations not already mentioned included

Mantoux tuberculin test (1:1,000), positive (July 1937)

Bleeding time, 2 min 45 sec (normal up to 3 min)

Clotting time, 2 min 4 sec (normal up to 2 min)

Fragility of red cells, trace at 0.45 per cent saline, complete at 0.3 per cent

Platelets, 132,000 per c mm (July 1938)

Benzidine test for occult blood in the stools, positive, after haematemesis

Case 3. Girl. Born 4.5.1937, died 20.3.1946. The parents were English and both healthy. The patient was the second of three children, the other two being healthy. She had had broncho-pneumonia at three years, chicken-pox and measles, and tonsillectomy at six years. Since the age of seven years, at intervals of three or four weeks, there had occurred attacks characterized by cough, shortness of breath, fever, and pallor. They had been heralded by a dry cough, the temperature had risen to 104°F , and the child had quickly become breathless and severely prostrated. Each attack had lasted from one to five days, and had been followed by a variable degree of anaemia, which at one time lowered the haemoglobin to 28 per cent, and the red cells to 2,500,000 per c mm. There was a history of slight haemoptysis in one attack. On 12.11.45, when eight years old, the child was admitted to The Hospital for Sick Children, and remained under observation until her death. On admission, she was thin and sallow, weighing only 40 lb. There was neither cyanosis nor finger clubbing. Physical examination was negative except for a few fine râles at the base of both lungs. In particular, the heart was normal, and there was no enlargement of the liver, spleen, or lymphnodes. The urine was normal. An X-ray of the chest showed widespread mottling over both lungs, reminiscent of the appearances seen in chronic congestive heart-failure. During four months in hospital the child experienced 10 attacks, death occurring during the last attack. They were ushered in by pain in either the chest or abdomen, and by coughing. Within a few hours the temperature reached 102° to 104°F , the pulse rose to 160, and the respirations to 60. There was moderate cyanosis. Air-entry over the bases

A blood count in February 1946 showed red cells 4,900,000 per c.mm, haemoglobin 105 per cent, white cells 14,460 per c.mm, and differential count of polymorphonuclears 38 per cent, lymphocytes 38 per cent, monocytes 6 per cent, and other cells 18 per cent

The child's serum gave a positive cold agglutinin reaction up to a titre of 1/128

Case 6 Girl Born December 1941 The parents and an older child were in good health Previous illnesses included 'bronchitis' for long periods every winter since birth, 'pneumonia' in infancy, and dysentery with blood in the stools at two and a half years At four and a half years the child had one or two attacks of cyanosis, was easily fatigued, had a rapid pulse-rate, complained of abdominal pain, and vomited once She became very pale The liver and spleen seemed of normal size The cardiac dullness was increased, and a localized systolic murmur was audible at the apex. A blood count showed red cells 2,300,000 per c mm, haemoglobin 40 per cent, reticulocytes 2.3 per cent, and white cells 7,300 per c mm The condition at first was thought to be one of hypochromic anaemia Three months later, there was an exacerbation of fatigue, and considerable coughing, with haemoptysis and streaks of blood in the sputum on several occasions over the next few months There were no abnormal physical signs detected in the lungs, but an X-ray showed soft fluffy mottling in all zones, enlargement of the heart, and a prominent pulmonary conus The spleen did not become palpable At the last examination in March 1947, when the child was aged five years and three months, there had been no further haemoptysis, and the mottling of the lungs seen in X-rays was diminished, but still present On iron-medication the red cells had risen to 3,800,000 per c mm The general condition was improved but the child still tired easily

Investigations included

Mantoux tuberculin test, negative

Wassermann reaction, negative

Blood-sedimentation rate, 11 mm in 1 hour

Marrow puncture, normal

Fragility of red cells, normal

Van den Bergh, indirect reaction, 1.7 mg bilirubin per 100 c c

Cold agglutinins on two occasions present in a titre of 1 in 2 and 1 in 4

Case 7 Boy Born 24.12.1943 He was an only child His parents were alive and well He was first admitted to The Hospital for Sick Children when 10 months old, on account of anaemia His weight was 13 lb The tip of the spleen could be felt, but otherwise there were no abnormal physical signs, and in particular the heart and lungs were normal There was no evidence of rickets The red cells numbered 3,800,000 per c mm, and the haemoglobin was 43 per cent An X-ray of the chest showed patchy consolidation throughout both lungs, with some collapse at the right base A blood transfusion of 180 c c was given The boy remained under observation during the next 18 months, usually in hospital in an oxygen tent During this period he underwent several attacks characterized by cough, fever of three or four degrees, cyanosis, and breathlessness, the respiration rate mounting to over 100 and the pulse-rate to 150 During these attacks moist sounds could be heard over both lungs, and there were often signs of consolidation at the right base Frequent X-rays confirmed the appearance of consolidation, together with mottled opacities in the rest of the lung fields Haemoptysis did not occur Anaemia was a constantly recurring feature, the red cells usually numbering about 4,000,000 per c mm

Blood count, red cells 2,800,000 per c mm, reticulocytes 1.6 per cent, no spherocytes, haemoglobin 30 per cent, white cells 8,600 per c mm, and a differential count of polymorphonuclears 66 per cent, lymphocytes 30 per cent, and eosinophils 4 per cent

Blood group, O Rhesus negative

Fragility of red cells, trace at 0.51 per cent saline, complete at 0.33 per cent

Wassermann and Kahn reactions, negative

Blood-sedimentation rate, 15 mm in 1 hour

Cold agglutinins, with own cells at 4°C, 1/32, at 37°C, negative, with Group O cells at 4°C, 1/8, at 37°C, negative

A second cold agglutinin test was negative

Serum-cholesterol, 104 mg per 100 c c

X-ray of skull and long bones showed no abnormality

Alkaline plasma-phosphatase 10 units (normal)

Serum Takata-Ara reaction, negative

After a blood transfusion of 1,300 c c, the haemoglobin rose to 80 per cent. A sternal puncture then showed a normal bone-marrow. Within three weeks anaemia was again becoming apparent, and the haemoglobin level had dropped to 55 per cent. Search for any site of bleeding was negative, and there was no sputum or vomitus. Several examinations of the stools for occult blood were negative, and repeated urine examinations were normal. A haemolytic process seemed most likely, the serum-bilirubin being raised to 2.1 mg per 100 c c, and the urinary urobilinogen being increased. Splenectomy was undertaken on 19.10.45 by Mr Charles Donald, the post-operative course being uneventful. For six months since her operation, anaemia has been a less severe feature, the haemoglobin varying between 70 and 90 per cent. During this period the child has been receiving iron, and injections of 2 c c of Campolon twice a week. She has, however, had frequent colds, and on several occasions two or three days of fever up to 101°F, accompanied by breathlessness and pallor, together with frequent haemoptyses, the first haemoptysis occurring in December 1945. Between attacks the child is seemingly normal.

Case 5 Girl Born June 1940. She was the only child of healthy non-consanguineous parents. The child had an attack of jaundice when two and a half years old, and clinical characters of the attack being those of acute infective hepatitis. Since the age of three and a half years there had been recurrent attacks of fever of three or four degrees, lasting a week or two, and accompanied by cough, with breathlessness, and the production of sputum often discoloured brown, and usually small haemoptyses. During an attack of whooping-cough at four years, the child was said to have coughed up blood with each paroxysm. Anaemia had not been a prominent symptom. Examined at five years old, the girl was well nourished and weighed 46 lb. The heart was normal. There was slight clubbing of the fingers. No mediastinal displacement was noted. Air entry was considered to be poor over the whole of both lungs, and coarse moist sounds were audible over each side of the chest. The throat was clean, the tonsils having been removed a year previously. The liver was of normal size, and no enlargement of the spleen or lymphnodes could be made out.

The following investigations were carried out:

Mantoux tuberculin test (1:1,000), negative

Sputum examination showed a few pus cells, but no tubercle bacilli or fungi

X-ray examination showed originally some mottling over the right lung, but in later films mottling extended throughout both lungs

The bronchogram appeared normal

TABLE III
Haematological Details of Seven Cases from The Hospital for Sick Children (1938 to 1947)

Case number	Sex	Red cells (per c mm)	Haemoglobin (%)	Colour index	Hypochromia	Anisocytosis and poikilo- cytosis	Reticulocytes (%)	Nucleated red cells (% of white cells)	White cells (per c mm)	Eosinophils (%) (per c mm)	Platelets (per c mm)	Bleeding time and clotting time	Red cell fragility	Cold agglutinins 1/8
1	Female	2,300,000 to 5,300,000	40 to 90	0.6 to 1.06	+	+	0.6 to 22	6	5,300 to 9,800	0 to 0 (0 to 585)	120,000	Normal	Normal	1/8
2	Male	2,100,000 to 3,300,000	16 to 70	0.83 to 1.07	+	+	11.6 to 26.4	2	10,000 to 18,600	0 to 2 (0 to 200)	132,000	Normal	Normal	1/10,000,000
3	Female	2,900,000 to 3,300,000	60 to 92	0.78 to 1.05	+	+	7 to 16	0	8,800 to 41,200	1 to 5 (200 to 450)		Normal	Normal	1/32
4	Female	5,600,000 to 2,800,000	30 to 90	0.55 to 1.03	+	+	1.0 to 13	1	5,500 to 13,400	0 to 11 (0 to 1,070)				1/128
5	Female	5,100,000 to 4,900,000	105	1.06	+	+	2.3	0	12,400 to 14,450 5,500 to 16,800	0			Normal	1/4
6	Female	2,300,000 to 1,000,000	10 to 90	0.8 to 1	+	+	0.6 to 1.4	0	8,900 to 14,800	0 to 4 (0 to 580)	617,000		Normal	0
7	Male	3,500,000 to 5,200,000	13 to 100	0.57 to 1.1	+	+								

The tip of the spleen was constantly palpable Clubbing of the fingers was present in the first period, but has since disappeared

Investigations

Mantoux tuberculin test (1 1,000), negative

Wassermann and Kahn reactions, negative

Van den Bergh direct test, negative, indirect test, faint trace

Several examinations of the blood for spherocytes were negative

In addition to the anaemia already mentioned, the white cells averaged from 9,000 to 14,000 per c mm, the polymorphonuclears averaging 40 per cent, and the lymphocytes 60 per cent

The reticulocytes were 1 to 2 per cent

Special staining showed no siderocytes

Cold agglutination tests were negative

Serum-cholesterol, 113 mg per 100 c c

Urine normal

Occult blood tests on the stools were negative

He has been under observation since, and in the last 12 months has been apparently in excellent health, without any signs of an attack Chest X-rays still show fine mottled shadows, especially of the right middle and lower lobes, but much less dense than formerly

TABLE II

*Clinical Details of Seven Cases from the Hospital for Sick Children
(1938 to 1947)*

Case number	Sex	Age at onset (years)	Present state	Haemoptysis or haematemeses	X ray pulmonary shadows	Cardiac enlargement	Palpable liver and spleen
1	Female	2	Alive, aged 13 years, Condition still active	+	+	+	+
2	Male	3	Died at 4½ years	+	+	+	+
3	Female	7	Died at 10 years	+	+	0	0
4	Female	1½	Alive, aged 7½ years Condition still active	+	+	0	0
5	Female	3½	Alive, aged 7 years Condition still active	+	+	0	0
6	Female	? early infancy	Alive, aged 5½ years Improved	+	+	+	0
7	Male	1½	Alive, aged 3½ years Good health	0	+	+	+

Discussion of Tables II and III Table II indicates the presence of abnormal pulmonary shadows in all the cases from The Hospital for Sick Children, the occurrence of haemoptyses or haematemeses in all but one of the cases, and the cardiac and hepato-splenic enlargement in the active phases of about half the cases Table III gives the range of haematological values, and in general it may be said that the lower figures relate to active stages of the disease, and the higher figures to quiescent phases The conclusions are in agreement with those derived from the survey of the cases published elsewhere, the anaemia is usually of a secondary hypochromic type, and tends to subside in remissions, especially if aided by iron therapy In addition, certain features indicate a haemolytic type of anaemia, such as reticulocytosis, the presence of nucleated red cells in the

TABLE III
Haematological Details of Seven Cases from The Hospital for Sick Children (1938 to 1947)

Case number	Sex	Red cells (per c mm)	Haemoglobin (%)	Colour index	Anisocytosis and poikilocytosis	Reticulocytes (%)	Nucleated red cells (% of white cells)	White cells (per c mm)	Eosinophils (%) (per c mm)	Platelets (per c mm)	Bleeding time and clotting time	Red cell fragility	Cold agglutinins 1/8
1	Female	2,300,000 to 5,700,000	40 to 90	0.6 to 1.06	+	0.6 to 22	0	5,300 to 9,800	0 to 9 (0 to 585)	120,000	Normal	Normal	1/8
2	Male	2,100,000 to 5,700,000	16 to 70	0.83 to 1.07	+	11.6 to 26.4	2	10,000 to 18,000	0 to 2 (0 to 200)	132,000	Normal	Normal	1/34 1/10,000,000
3	Female	2,900,000 to 3,300,000	60 to 92	0.78 to 1.05	+	7 to 16	0	8,800 to 41,200	1 to 5 (200 to 450)		Normal	Normal	1/32
4	Female	5,000,000 to 2,800,000	30 to 90	0.55 to 1.03	+	1.6 to 13	1	5,500 to 13,400	0 to 1.4 (0 to 1,070)			Normal	1/128
5	Female	5,100,000 to 1,900,000	105	1.06	+	2.3	0	12,400 to 14,450 5,500 to 10,800	0			Normal	1/4
6	Female	2,300,000 to 3,500,000	40 to 90	0.8 to 1	+	0.6 to 1.4	0	8,000 to 14,800	0 to 4 (0 to 560)	617,000		Normal	0
7	Male	1,000,000 to 5,200,000	13 to 100	0.57 to 1	+								

circulating blood, slight jaundice, indirect positive van den Bergh reaction, slight increase in urinary urobilinogen, and the presence of cold auto-agglutinins in active phases. Low figures or absence of cold agglutinins in Table III relate to quiescent phases. Absence of methaemalbumin, however, indicates extravascular blood destruction. Reticulocytosis is also a normal response to blood loss. An increase in serum-bilirubin and urinary urobilinogen can be accounted for by pulmonary haemorrhage and inability of the engorged liver to deal with excessive blood pigments. The development of cold auto-agglutinins (which has not been reported previously) is interpreted as an antibody response to the destruction of the red blood corpuscles shed into the child's lungs. In conclusion, the anaemia may be interpreted as the result of recurrent pulmonary haemorrhages, and the peculiar pseudo-haemolytic features of the anaemia are explained by the fact that blood is not shed outside the body, but within it, that is, into the lungs.

Post-mortem Reports

Case 2 (P M 193/36) A boy aged four years three months. The body of a tall boy (the height of a boy of six years), of normal weight, fairly well covered. The brain and meninges were normal. No pus was found in either middle ears or mastoids. The cervical lymphnodes of the left side were enlarged. There was no fluid accumulation in the pleural sacs, and the visceral and parietal pleurae were normal. The lungs did not collapse on opening the pleural cavities, they were congested, dark purple, and heavy. There were many darker areas, presumably haemorrhages, giving the lungs a mottled appearance. The left lower lobe and the right middle lobe appeared to be particularly solid. The trachea and bronchi contained a considerable amount of haemorrhagic fluid. There was a large inferior tracheo-bronchial lymphnode on the left side and a smaller one on the right. The left superior tracheo-bronchial and broncho-pulmonary lymphnodes were enlarged, greyish-brown, and of moderate consistency. The heart was hypertrophic (weight 100 gm, expected weight 75 gm) and dilated. The myocardium was flabby. There were no congenital lesions and the valves were normal. The liver was moderately enlarged, firm, greyish-brown in colour, and homogeneous in appearance. The spleen was slightly enlarged, and the Malpighian bodies very prominent. The kidneys were pale, but otherwise normal. The gastro-intestinal tract was normal. The mesenteric lymphnodes were increased in size and number.

Histological report Material was selected from representative parts of both lungs. The pleura over the left lower and right middle lobe was thickened. Pleural capillaries were congested and there was evidence of frank haemorrhage into the pleura over the right middle lobe. A good number of haemosiderin-laden phagocytes lay between the collagenous pleural fibres over the left lower lobe. Most of the alveoli were stuffed with red blood-cells, haemosiderin-laden histiocytes, multinucleate cells with pigment, and free haemosiderin granules, the airspaces being almost completely replaced. Some alveoli were lined by cuboidal cells containing haemosiderin granules. Recent haemorrhage and deposits of pigment alternated in different parts of the lungs. The alveolar walls were notably thickened from cellular hyperplasia and increase in reticulin and collagen fibres, with numbers of pigment-laden histiocytes interspersed, but the elastic framework of the alveolar walls was greatly reduced with little evidence of degeneration. The general impression was that of hypoplasia of elastic tissue. Many interalveolar capillaries showed thickening of their walls, and were con-

gested The larger vessels were normal An occasional medium-sized vessel showed degenerative changes in the wall, namely, reduplication and fibrillation of the elastic fibres and hyalinization of the fibro-muscular layers The vessel walls showed no evidence of pigment incrustation Many bronchi and bronchioles, in particular in the right middle lobe, were filled with masses of polymorphonuclear cells, and the peribronchial tissue was formed by hyperplastic lymph follicles Some of the bronchial exudate was organized and young fibrous tissue projected into the lumen of these bronchi There was also fibrous thickening of the perilobular septa in the right middle lobe with numerous congested capillaries and evidence of frank haemorrhage The large left inferior tracheo-bronchial lymphnode showed hilar fibrosis, considerable follicular hyperplasia, and a few haemosiderin-laden phagocytes in the peripheral sinuses The liver showed shrinkage of liver cells and slight fatty degeneration in the centrilobular parts There was no evidence of haemosiderin deposition in liver cells or Kupffer cells The vessels were normal The spleen showed prominent Malpighian bodies The sinusoids were congested There were no haemosiderin deposits The kidneys, heart muscle, adrenals, and bone-marrow were normal

Summary The principal changes were to be found in the lungs, consisting of considerable interstitial fibrosis, associated with evidence of recent intra-alveolar haemorrhage, as well as old haemorrhage followed by disintegration of red cells and conversion of haemoglobin into haemosiderin, which was both free in the tissue and in macrophages The vascular changes were distension and thickening of interalveolar capillaries, occasional hyaline degeneration of the fibro-muscular wall and disruption of elastic fibrils of medium-sized vessels, and the large vessels were normal In the right middle lobe there was bronchitis and bronchiolitis with some organization of inflammatory exudate The other organs were essentially normal for the child's age, and free from haemosiderin deposits, with the exception of an inferior tracheo-bronchial lymphnode which contained a little pigment

Case 3 (P M 345/99) A girl aged 8 years and 10 months The body was considerably underweight (32 lb) and of normal height (52 in) The skin showed marked waxy pallor The brain was normal, but the meninges congested The middle ears and mastoids were normal The cervical lymphnodes were large and grey, the tonsils were large and contained pus in the crypts There was a little clear yellow fluid (about 1 oz) in each pleural cavity There was patchy fibrinous pleurisy over both lower lobes and the right middle lobe The lungs did not collapse on opening the pleural cavities, they were heavy, voluminous, and of a greyish-brown colour, with scattered haemorrhages beneath the pleura The interstitial fibrous septa were well marked There was considerable consolidation of the lower lobes Carmine in gelatin was injected into the pulmonary circulation in an attempt to demonstrate vascular abnormalities Subsequent cross-sections through all the lobes of the lungs did not reveal any such evidence The broncho-pulmonary and inferior tracheo-bronchial lymphnodes of both sides and a right superior tracheo-bronchial lymphnode were large, grey, and of medium consistency The right cardiac chambers were slightly dilated, and the myocardium was pale, of normal consistency, and not hypertrophic There was no congenital lesion and the valves were normal The liver was enlarged, the inferior edge being one finger's breadth below the costal margin Its colour was brown, and consistency medium The appearance was not that of fatty degeneration The gall-bladder and bile passages were normal The pancreas was normal The spleen was enlarged, soft, and grey and the Malpighian bodies prominent The adrenals were normal The kidneys

showed some congestion of the pyramidal bases. The pelves, ureters, and urinary bladder were normal. The gastro-intestinal tract was normal. The right femur contained red bone-marrow throughout three-quarters of its length, except for the distal part. The corticalis was of normal appearance. Pieces of liver, spleen, and kidney gave a positive Prussian blue reaction, and so did a specimen of urine collected from the bladder.

Histological report. Material was selected from all lobes of both lungs. The pleura over both lower lobes was formed by thickened oedematous connective tissue with numerous distended capillaries. Very few alveoli contained air. Most alveoli contained oedematous fluid or masses of pigment-bearing macrophages or red blood-cells, as a result of recent haemorrhages. The epithelial lining of many airspaces had desquamated, others, however, were lined by pigment-laden cuboidal epithelium. The alveolar walls (interalveolar septa) were thickened, from increase in reticulum and collagen, and the alveolar ducts showed hypertrophied smooth muscular bundles. Elastic fibres had completely disappeared from the walls of many alveoli. In other parts they showed varying degrees of degeneration, they were often torn, fibrillated, or appeared as plump, star-like bodies. In many instances foreign-body giant cells were apposed to such degenerated fibres, which stained deep blue with haematoxylin, greyish-black with elastic stains, and faint to medium blue with Prussian blue, but they did not stain with von Kossa's and purpurin stains for calcium. They appeared, therefore, to be formed of degenerated organic matter (elastic tissue) and were encrusted with iron salts. The interlobular septa were moderately thick and formed by oedematous loose connective tissue with numerous distended capillaries. The interalveolar capillaries were particularly tortuous and congested, some of them appeared to be stretched longitudinally, others bulged into the alveolar lumina. Small and medium-sized vessels were also elongated and stretched in appearance, and they showed fibrillation and disruption of elastic fibres in their walls, with foreign-body giant cells apposed to them. Some giant cells had surrounded and engulfed the degenerated fibres, which were coated with iron salts and showed the staining reactions indicated above. The fibro-muscular parts of the vessel walls showed evidence of hyaline degeneration. The trachea, bronchi, and bronchioles were particularly free from infection throughout, and the absence of infection from the alveoli was equally striking. The broncho-pulmonary, superior and inferior tracheo-bronchial, and paratracheal lymphnodes showed sinus catarrh and the presence in the peripheral and central sinuses of haemosiderin-laden macrophages. Some foreign-body giant cells with degenerated iron-coated elastic fibres were found in the sinuses of the broncho-pulmonary lymphnodes. The upper cervical lymphnodes were normal. Sections of myocardium from the left and right ventricles were normal. Sections of aorta, internal carotid artery, pulmonary artery, pulmonary vein, and superior and inferior vena cava showed no abnormality of elastic tissue or other wall structures. The liver showed congestion of the central veins and sinusoids. The liver cells and Kupffer cells were free from haemosiderin. The spleen showed no increase in reticulum. The Malpighian bodies were normal. The pulp contained numerous red blood-cells, but there was no haemosiderin pigment. The kidneys, adrenals, pancreas, intestines, and mesenteric lymphnodes were free from haemosiderin. Sections from various parts of the brain, pituitary, submaxillary glands, thyroid, tongue, epiglottis, oesophagus, ovaries, skin, skeletal muscle, and diaphragm showed no evidence of deposition of haemosiderin pigment.

Summary. The main changes were to be found in the lungs. There was fibrous thickening of the pulmonary interstitial tissue, degeneration of the elastic fibres

in the alveolar walls, and massive infiltration of the air sacs and alveolar walls with free haemosiderin pigment and haemosiderin-laden macrophages. The interalveolar capillaries were stretched and congested, whilst small and medium-sized arteries and veins showed degenerative changes of the elastic fibres. Giant cell phagocytes were apposed to and surrounding the degenerated fibres, and some were found in the regional lymphnodes. No evidence of haemosiderosis was found in any other tissue.

Discussion of Table IV Some authors give histological data on the lungs in great detail, others merely mention their conclusions. It is difficult to compare cases when investigations and descriptions vary so much. At the same time, Table IV shows a number of features common to all cases. Even the youngest cases show evidence of capillary stasis and the aggregation of heart-failure cells, as well as fresh red blood-cells in the alveolar spaces. Thickening of fibromuscular elements in interalveolar septa is slight to start with, and tends to progress with age. Equally, changes in the elastic fibres may be absent or so slight as to be interpreted as absent. When changes progress, the abnormalities in elastic tissue become more prominent, fragments become coated with yellow iron pigment, or with an organic iron compound staining blue with haematoxylin. Foreign-body giant cells become apposed to the fragments, engulf them, and remove them by the regional lymphnodes. Interalveolar capillaries tend to be dilated and tortuous, and small and medium-sized arteries and veins may show hyaline degeneration of collagen and muscle, as well as disruption of elastic. Larger vessels are hardly affected at all, and the pulmonary artery is always normal. The bronchi are free from pneumonic exudate as a rule, and so are the alveolar spaces.

Discussion

The condition of pulmonary haemosiderosis, or essential brown induration of the lungs, appears to be one commencing usually in early childhood, often in infancy. There appears to be no hereditary or familial predisposition. The clinical signs, once recognized, are fairly typical, and are characterized by periodic attacks of dyspnoea and cyanosis, associated with hypochromic anaemia with haemolytic features. Haemoptyses, haematemeses, and abdominal pain may be present. Physical signs in the chest are insignificant by comparison with radiological signs, which tend to improve and relapse. The pathology is remarkably uniform in all the cases examined, and throws light on the aetiology and pathogenesis of the condition. Changes are confined to, or maximal in, the lesser circulation. Myocardial changes, if present, are insufficient to account for the pulmonary lesions. Anaemia is certainly secondary, and in some instances there is even a compensatory rise in the red-cell count when anoxaemia with dyspnoea and cyanosis supervenes in the final stages of the disease (Hanssen, 1947). Acquired inflammatory changes and subsequent carnification are usually absent. Increase of reticulin, collagen, and muscle, and decrease of elastic fibres in the pulmonary interstitial tissue leads to lack of distensibility of the lungs with consequent peripheral stasis in the capillary bed. This is followed by haemosiderin-laden macrophages and giant cells.

TABLE IV
Histology of Lungs

Case	Age (years)	Interalveolar septa			Alveolar content	Alveolar capillaries	Other pulmonary vessels	Bronchi
		Collagen, muscle	Elastic					
Ceelen (1931)	1	Marked hypertrophy	Hypoplasia Fragmentation Giant cell pha- gocytosis	Heart failure cells Red cells. Some polymor- phonuclears				Peribronchial fibrosis Round cell infiltra- tion Pigment histo- cytes in lumina and walls
" "	2							
Montaldo (1938)	2	Fibrous thickening	Slight reduction	Heart failure cells Some multinucleato cells	Dilatation	Normal		Muscular hypertrophy of bronchioles Pig- ment histiocytes in lumina
Anspach (1939)	7	Fibrous thickening		Heart failure cells Red cells		Neerotizing arteritis		
Gellerstedt (1939)	15	Fibro muscular thickening	Hypoplasia Fragmentation Giant cell pha- gocytosis	Heart failure cells Red cells Few polymor- phonuclears	Dilated Tortu- ous Cells in walls increased	Small vessels—cells in wall increased Elastic increased in small veins		Pigment histiocytes in bronchioles
Belfrage (1943)	19	Thickened	Fragmentation	Heart failure cells Red cells	Dilatation			
Glanzmann and Walthard (1941)	11	Fibro muscular thickening	Hypoplasia Fragmentation Giant cell pha- gocytosis	Heart failure cells Red cells Some polymor- phonuclears	Dilated Tortu- ous Separu- tion of endo- thelial cells Loss of elastic in vicinity			Muscular hypertrophy Elastic increased or fragmented Pigment histiocytes in lumina
Pilcher and Etzgen (1944)	6½	Fibrous thickening	Fragmentation Giant cell pha- gocytosis	Heart failure cells Red cells	Dilatation Thickening of walls	Small vessels thick- ened Iron coating of elastic Large vessels normal		Macrophages in lumi- na Fragmentation of elastic

Fibro muscular thickening

Hypoplasia Fragmentation

Heart failure cells Red cells

Dilatation

Scheidegger and Dreyfus (1915)

Slight fibrous thickening

Normal

Reyo (1915)

Fibro muscular thickening Cellular hyperplasia

Hypertrophy

Heart failure cells, some multinucleate cells Red cells

Present Series, Case 2

Thickening of reticulin and collagen Cellular hyperplasia

Hypoplasia Some fragmentation

Heart failure cells Red cells

Dilatation

Normal

Pigment in bronchial epithelium

Normal arteries and veins Occasional iron coating of collagen and elastic

Hyaline thickening and fatty infiltration of walls Iron coating of elastic

Macrophages in lumen

Thickening of reticulin, collagen, and muscle

Fragmentation Giant cell phagocytosis

Heart failure cells Red cells

Dilatation and thickening

Heart failure cells, some multinucleate cells Red cells Some polymorphonuclears

Large vessels, normal Medium vessels, occasional hyaline degeneration of collagen and muscle Fragmentation of elastic

Purulent exudate Fibrous organization

Dilated Tortuous Stretched Separation of endothelial cells

Large vessels, normal Small and medium vessels, fragmentation and iron coating of elastic

Normal

Changes are slight to start with, which accounts for the insidious onset of the disease. The intermittent periodic course and the increasing severity of the clinical picture are explained by the fact that ever larger portions of the lungs become affected. Anoxaemia supervenes, and leads to dyspnoea and cyanosis. Haemoptyses and haematemeses may occur. Subpleural haemorrhages, particularly in the region of the diaphragm, may give rise to referred abdominal pain. Haemosiderin deposits, fibrosis, and areas of collapse are the pathological basis of the radiological appearances. Pulmonary haemosiderosis is not part of a generalized haemosiderosis, and has no relation to haemochromatosis, since there is no general disturbance of iron metabolism. The prognosis in the condition is bad, as in our series of seven cases, although five are alive, in only one case can the general state of the child be said to be good. In all five cases the X-ray appearances of the lungs are still obviously abnormal.

Summary

1 Seventeen cases of idiopathic pulmonary haemosiderosis are presented from the literature.

2 To these, seven more are added, collected at The Hospital for Sick Children, Great Ormond Street.

3. The clinical, radiological, and haematological features are discussed, and a well-defined diagnostic entity is presented.

4 The morbid anatomy is reviewed, and implications on aetiology and pathogenesis discussed.

The authors acknowledge their thanks to Dr Donald Paterson for permission to include Cases 2, 4, and 6. Case 4 has been described in *Proc Roy Soc Med* (1946), 39, 131. We are indebted to Mr V C Conlay for the histological preparations, to Mr E V Willmott for the photomicrographs, and to Miss Eileen Rawlings for clerical assistance.

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FIG 1 Case 7 X ray of the chest, showing patchy consolidation throughout both lungs, with some collapse at the right base





FIG. 3 Case 3 Section of lung stained by hematoxylin and eosin ($\times 80$) General survey of brown lung induration, numerous heart failure cells, plump elastic rods, irritation giant cells, and thickening of alveolar walls

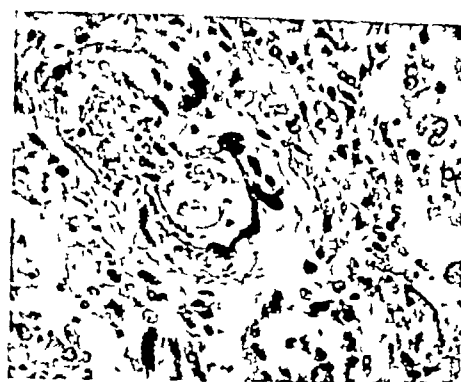


FIG. 4 As Fig. 3 ($\times 300$) Interalveolar capillary in thick alveolar wall. Vascular endothelium separated from alveolar space which is crowded with macrophages (anoxaemia). Elastic fibres engulfed by giant cells, in apposition to capillary



FIG. 5 Section of normal lung from a child aged 5 1/2 years, silver impregnation stain ($\times 400$)



FIG. 6 Case 3 Section of lung, silver impregnation stain ($\times 400$) Shows increase in reticulum (collagen precursor) in alveolar walls



FIG. 7 Section of normal lung from a child aged 8 1/2 years, stained by van Gieson ($\times 400$)



FIG. 8 Case 3 Section of lung, stained by van Gieson ($\times 400$) Shows increase in collagen in alveolar walls

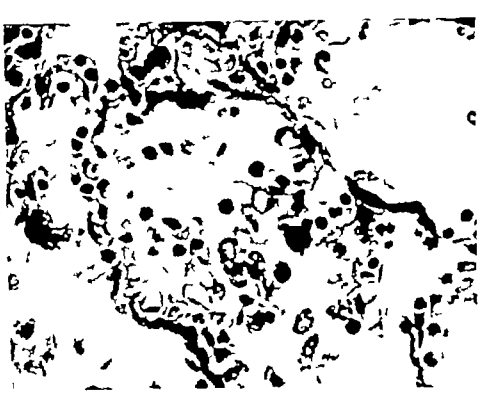


FIG. 9 Section of normal lung from a child aged 8½ years, stained for elastic fibres ($\times 400$)

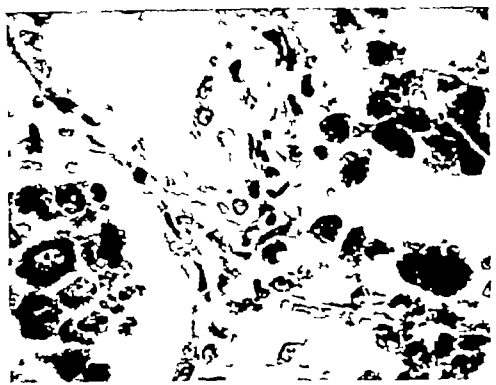


FIG. 10 Case 3 Section of lung, stained for elastic fibres ($\times 400$) Area shows hypoplasia of elastic elements in alveolar walls

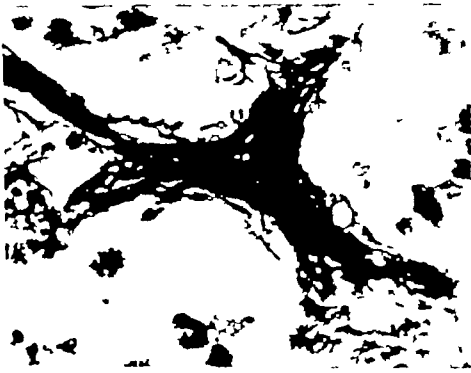


FIG. 11 Case 3 Section of lung, stained for elastic fibres ($\times 400$) Area shows plump, star like elastic body at junction of alveoli



FIG. 12 Section of normal lung from a child aged 8½ years, stained for elastic fibres ($\times 400$) Area shows elastic fibres in wall of small vein

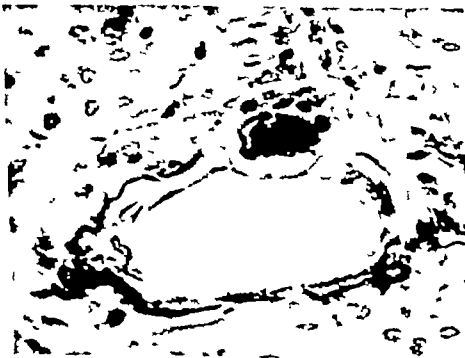


FIG. 13 Case 3 Section of lung stained for elastic fibres ($\times 400$) Area shows small vein of size comparable to that in Fig. 12 Showing degeneration and rupture of elastic fibres in vessel wall. Phagocytosis of curled up elastic material by irritation giant cell in apposition to vessel wall



FIG. 14 Case 3 Section of bronchio-pulmonary lymph node, stained by haematoxylin and eosin ($\times 145$) Area shows degenerated elastic fibres, giant cells, and haemosiderin laden macrophages in peripheral sinuses of lymph node

THE TREATMENT OF ARSENICAL DERMATITIS WITH DIMERCAPTOPROPANOL (BAL)¹

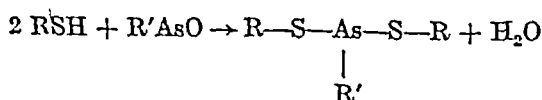
BY A B CARLETON, R A PETERS, AND R H S THOMPSON

(From the Department of Dermatology, the Radcliffe Infirmary, and the
Department of Biochemistry, Oxford)

With Plates 5 to 9

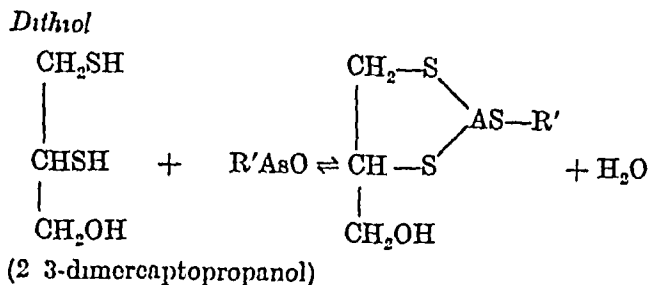
BIOCHEMICAL investigations into the mode of action of the arsenical blister gases during the recent war led to the discovery of a compound, 2 3-dimercaptopropanol, which was highly effective in preventing vesication in skin contaminated with arsenical gases, such as lewisite, and also in the treatment of the systemic effects resulting from absorbed arsenic in experimental animals heavily contaminated with lewisite (Stocken and Thompson, 1941, Peters, Stocken, and Thompson, 1945, Stocken and Thompson, 1946) The action of this compound lies in its ability to react with arsenoxides to form relatively stable compounds, thereby bringing about the removal of arsenic from its combination with the tissue acceptors, and causing ultimately its excretion in the urine This substance came, therefore, to be known as British Anti-Lewisite or BAL, a name given to it by the American workers in this field, in this country it was also known as OX 217, as it was undesirable for security reasons to publish its chemical name at that time² Experimental work upon the same lines with enzyme systems and laboratory animals soon showed that the compound was also able to diminish the toxicity of the therapeutic arsenoxides (Eagle, 1943, Stocken, Thompson, and Whittaker, 1947) The efficiency of this dithiol compound in the treatment of the toxic effects of arsenicals as compared with the monothiols studied in the past (Voegtlin, Dyer, and Leonard, 1923, 1925, Walker, 1924, Rosenthal and Voegtlin, 1930, Voegtlin, Rosenthal, and Johnson, 1931) is due to the greater stability of the cyclic compound formed between the dithiol and the arsenical as compared with the open-chain compound formed with monothiols

Monothiol



¹ Received August 8, 1947 A Report to the Medical Research Council

² The Council on Pharmacy and Chemistry of the American Medical Association has recently (1946) recommended the adoption of the non proprietary name of Dimercaprol (Q.J.M. New Series No 65)



The five-membered ring formed with the dithiol must also be more stable than the complex formed between the arsenical and the tissue acceptor, which in our view must itself comprise a dithiol grouping

The earliest application of dimercaptopropanol to the treatment of generalized arsenical dermatitis, as opposed to that of experimental or accidental contamination with arsenical vesicants, was carried out in 1943 by Longcope, Wintrobe, and Luetscher, who obtained promising results by the inunction of 5 per cent BAL ointment into six patients suffering from phenarsazine chloride dermatitis. Eagle (1943) next reported a series of cases of dermatitis occurring in the course of arsenotherapy in which a beneficial effect was obtained by intramuscular injection of a 5 per cent solution of BAL in arachis oil and benzyl benzoate. Before the preparation by Eagle of oily solutions of BAL suitable for injection, work had been started in this country on the treatment of post-arsphenamine dermatitis by inunction of ointments, but on receiving a report of Eagle's advance (private communication), injection therapy was begun here, using an improved method of ampoule preparation (Peters, Stocken, and Thompson, 1944).

An account of the first 30 cases of arsenical dermatitis treated with dimercaptopropanol in this country has already appeared (Carleton, Peters, Stocken, Thompson, Williams, Storey, Levvy, and Chance, 1946),³ and the present report describes a further 44 cases.

Material

The 44 cases described here were collected through the co-operation of the Ministry of Health, the Service medical departments, and the clinicians concerned. Venereal disease clinics were notified of the availability of dimercaptopropanol for the treatment of complications of arsenotherapy, the Medical Research Council arranging for the distribution of the drug as needed. With four exceptions, the dermatitis was in all cases severe and widespread, showing in addition to erythema one or more of the following features, desquamation, exfoliation, oozing, or fissuring. Of the four milder cases, one (Case 8) presented a generalized maculo-erythematous rash with urticarial elements, the second (Case 13) a generalized toxic erythema with urticarial wheals and purpuric areas on the arms and legs, which was thought by the clinician to be the precursor of an acute exfoliative dermatitis, the third (Case 33) was described as

³ An account of this work was submitted to the War Office in 1944.

developing 'dermatitis and oedema of the face, arms and thorax', and the fourth (Case 37) showed 'bright red erythematous blotches on hands and feet, spreading up forearms and ankles, with oedema on backs of hands, ankles and eyelids' Photographs of Cases 7, 17, and 27 are given in Plates 5 to 9

Treatment

The ampoules used were prepared by Messrs Boots Pure Drug Co Ltd, under the supervision of Dr L A Stocken, and also by Messrs Burroughs, Wellcome, Ltd The ampoules each contained 2 c c of 5 per cent 2 3-dimercaptopropanol dissolved in arachis oil containing 10 per cent benzyl benzoate, they were nitrogen-filled and sterilized by heating for one hour at 170° C The drug was given by deep intramuscular injection into the gluteal region The recommended dosage, which was followed in all cases, except where stated in the case abstracts, comprised the following course of injections

First day one ampoule four times during the first 24 hours at four-hourly intervals

Second, third, and fourth days one ampoule twice daily, morning and evening

Fifth and sixth days one ampoule daily

In deciding on these final doses much help was given by trials on volunteers in the United States of America When possible, any other local treatment to the skin was avoided.

Results

In putting together the results of a clinical trial of this kind, the inevitable diversities in the nature of the clinical reports from the different clinics, and the varying severities of the cases studied, render it difficult to assess the results on an exactly quantitative basis It has been decided, therefore, to include, as well as a semi-quantitative numerical assessment of the progress, brief abstracts of each of the clinical reports so that some idea of the type of lesion and of the progress made can be obtained from the clinicians' own accounts of the cases under their care Table I provides a summary of the responses obtained to therapy with BAL As an indication of the duration of the condition the number of days that elapsed between the first injection of BAL and the stage of healing mentioned in the Table is given As some records were vague regarding the exact date when symptoms of skin irritation first appeared, it was felt that in giving the length of time before recovery a better assessment would be provided by starting from the beginning of BAL therapy rather than the beginning of the dermatitis It should be pointed out, however, that in the majority of cases injection therapy was commenced within a few days of the development of severe generalized skin changes Basing an initial rough analysis on the general clinical impressions of the cases, the responses obtained with dimercaptopropanol therapy may be divided into the following groups

	<i>Number of Cases</i>
Good response	23
Fair response	8
Doubtful response	7
No response	3
Patient died	3

TABLE I

Summary of Responses to Therapy with BAL

<i>Case</i>	<i>Stage of healing reached</i>	<i>Number of days after first injection of BAL</i>
1	Discharged	34
2	Skin normal except for cracks in palms of hands and soles of feet	20
3	Skin clear except for neck and under eyes	13
4	Skin normal	22
5	Skin normal except for peeling on hands and soles	21
6	Discharged	36
7	Skin normal except for scaling on backs of heels	33
8	Discharged	12
9	Skin normal	22
10	Skin normal	42
11	Ready for discharge	46
12	Discharged	11
13	Discharged	16
14	Skin almost normal	24
15	Skin condition slowly improved	
16	Died	
17	Skin almost normal	28
18	Erythema and desquamation decreased	16
19	Practically full recovery	27
20	Skin satisfactory	30
21	Skin very satisfactory, but scaling	28
22	Slow progress, no dates given	
23	Skin normal	20
24	Skin normal except for small moist patches on thighs	10
25	Skin normal	26
26	Skin still red and scaly	15
27	Skin practically normal	22
28	Skin normal	28
29	Skin normal except for mottling on chest and abdomen	29
30	Patient left hospital	
31	Patient left hospital Arms and legs pigmented Palms scaling	10
32	Skin normal	17
33	Mild case Skin almost normal	7
34	Skin nearly normal	23
35	Skin normal	9
36	Skin normal	14
37	Mild case Skin normal	6
38	Died	
39	Skin normal except for weeping of scalp	13
40	Died	
41	Skin practically normal	26
42	Skin normal except for some pigmentation	17
43	No date given for healing or nearly complete healing	
44	Discharged	15

It will be seen that three cases of the series (Nos 16, 38, and 40) ended fatally. Case 16 at autopsy showed oedema of the lungs with early bronchopneumonic consolidation of both lower lobes. Case 38 became pyrexial and delirious,

finally developing signs of uraemia, while in Case 40 death was certified as 'resulting from toxæmia from widespread impetigo occurring in secondary syphilis, with exfoliative dermatitis due to intravenous N A B' In the latter two cases, however, a considerable improvement in the condition of the skin was reported prior to death. In four cases (Nos 15, 22, 30, and 43) it was impossible to assess the number of days that elapsed between the start of therapy and healing or nearly complete healing, in three of these cases insufficient data were provided, while the fourth case left hospital against advice 17 days after the first injection and suffered a relapse. Excluding these four

TABLE II

Duration of Signs after commencement of Therapy with Dimercaptopropanol

Patients reported finally as fit for discharge or with normal skin		Patients whose final report indicated skin nearly normal, but with some residual changes still present	
Case	Number of days after first injection of BAL	Case	Number of days after first injection of BAL
1	34	2	Skin normal except for cracks in palms of hands and feet 20
4	22	3	Skin clear except on neck and under eyes 13
6	36	5	Skin normal except for peeling on hands and soles 21
8	12	7	Skin normal except for scaling on backs of hands 33
9	22	14	Skin almost normal 24
10	42	17	Skin almost normal 28
11	46	18	Erythema and desquamation decreased 16
12	11	19	Practically full recovery 27
13	16	20	Skin normal except for numerous furuncles 30
23	29	21	Skin very satisfactory, though still dry and scaling 28
25	26	24	Skin normal except for small moist patches on thighs 10
28	28	26	Skin still red and scaly 15
32	17	27	Skin normal except for peeling on face 22
35	9	29	Skin normal except for mottling on chest and abdomen 29
36	14	31	Patient left hospital. Arms and legs pigmented. Palms scaling 10
37	6	33	Skin almost normal 7
44	15	34	Skin almost normal. No erythema though slight desquamation 23
Mean	22.7	39	Skin normal except for weeping of scalp 13
		41	Skin almost normal 26
		42	Skin normal except for some pigmentation 17
		Mean	20.6

cases and the three with a fatal termination, it was found that the mean number of days between the first injection of dimercaptopropanol and healing or practically complete healing for the remaining 37 cases was 21.5 days (ranging from six to 46 days).

In Table II these 37 cases are divided into those patients reported as being finally fit for discharge, or whose skin was reported as normal, and those whose

final report indicated that the skin was nearly normal but in whom some residual abnormality still persisted. In Group 1 the mean time from the first injection till complete healing was 22.7 days (range six to 46 days) while the mean time for Group 2 was 20.6 days to the stage of healing described in the Table

Complications

It will be noticed from the clinical reports that in a proportion of cases abscesses developed in the buttocks and elsewhere. Since abscess formation at the injection site was also observed in a small number of cases in the series reported earlier, an analysis of the occurrence of this complication is given in Table III. In all, development of abscesses or boils either in the gluteal region or elsewhere occurred in 14 cases during their stay in hospital.

TABLE III

Case	Site of pyogenic complications
4	Subcutaneous abscess in left arm. Many follicular pustules in the beard and pubic areas. Discharging pressure sore over sacrum.
6	Abscesses at injection sites in right and left buttocks.
10	Large boils on right forearm and left thigh.
14	Sloughs on buttocks at sites of bisoxyl injections.
20	Abscesses in both buttocks.
21	Abscesses in both buttocks.
24	Abscess in left buttock.
26	Gluteal abscess stated to be due to faulty administration of penicillin.
28	Abscess in left buttock.
30	Boil in left axilla and another on buttocks.
31	Late abscess in left buttock.
35	Abscess in right buttock.
36	Abscess in both buttocks and right axilla present before starting BAL injections.
38	Abscess in right buttock.

It will be seen that in eight of these cases (Nos. 6, 20, 21, 24, 28, 31, 35, and 38) abscesses occurred at the sites of the BAL injections (it is assumed that the gluteal abscesses occurred at the injection sites), but that in a further six cases (Nos. 4, 10, 14, 26, 30, and 36) abscesses or boils occurred either at the sites of injection of other substances (Cases 14, 26, and 36) or elsewhere in the body. Apart from this complication the injections of dimercaptopropanol were well tolerated.

Discussion

In the series of 30 cases of arsenical dermatitis reported earlier (Carleton, Peters, Stocken, Thompson, Williams, Storey, Levy, and Chance, 1946) it was concluded from the clinical evidence that treatment with 2,3-dimercaptopropanol had brought about a beneficial effect in approximately 50 per cent. of the cases. This may be compared with a report of the Council on Pharmacy and Chemistry of the American Medical Association (1946) which stated that 'in 88 cases of arsenical dermatitis, of which 51 were of the exfoliative type, the administration of BAL usually stopped the progressing of the inflammatory reaction and accelerated the healing process. Twenty per cent. of the patients did not

respond to treatment' (See also Longcope, Luetscher, Wintrobe, and Val Jager, 1946)

In the present series of cases clinical assessment again shows that about 50 per cent were definitely benefited ('Good' responses obtained in 23 of the 44 cases), though if the eight cases in which a 'Fair' response was obtained are included, the number of those benefited by the treatment is 31 (70 per cent). In some cases an almost dramatic response was obtained, but since the action of dimercaptopropanol is directed specifically against the intoxicating metal it is to be expected that if any severe degree of secondary sepsis of the skin is present, BAL therapy will be unlikely to exert any obvious effect on this. We have not, unfortunately, been able to observe a series of control cases, in which BAL therapy was withheld, to contrast with the present series. Our mean duration of 21.5 days from the first injection of BAL to healing or nearly complete healing, however, appears to contrast well with the mean total duration of 62.5 days given by Davies (1943) for 135 cases occurring between 1929 and 1941. In the 51 exfoliative cases studied by Eagle (1946) it was claimed that the mean time for definite improvement in those cases which responded to treatment (80 per cent) was three days, the mean time for almost complete recovery being 13 days.

In our experience the changes in the skin which disappear earliest and most dramatically on treatment with BAL are the oedema and oozing, if present (e.g. Case 27). In view of the increased degree of capillary dilatation and permeability which is known to be induced by the presence of arsenic, these responses to BAL might be expected. The re-formation of the damaged, and possibly shed, keratin layer of the epidermis, however, must clearly also depend on other factors (nutrition, absence of coincidental infection, etc.), and hence a direct and dramatic response to specific anti-arsenical therapy would not be expected in these cases.

In a number of cases in the earlier series the urinary excretion of arsenic was followed, but, unlike the experiments with animals contaminated with large amounts of lewisite, no definite increase after treatment with BAL was observed. This is probably due to the day-to-day variations in arsenic excretion in the absence of BAL, and to the fact that these patients had mostly been receiving arsenicals of the type of Neoarsphenamine over long periods of time. It has been stated, on the other hand, that after therapy with Neoarsphenamine or Mapharside a definite increase in arsenic can be detected (Luetscher, Eagle, Longcope, and Watson, 1946). On account of our earlier negative findings, however, arsenic excretions were not followed in the present series.

The development of abscesses at the injection sites is in our opinion further evidence of the liability to transient bacteraemia in cases in which widespread infection of the skin is present, a view which is supported by the fact that in six further cases abscesses or boils developed unconnected with the BAL injections. The intramuscular injection of the oily solution of BAL will act as an irritant and may even induce some localized necrosis, and so form a suitable nidus for bacterial growth and abscess formation if a bacteraemia is also present.

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progress numerically In the remaining 37 cases the mean number of days between the first injection of BAL and healing or practically complete healing was 21.5 days

3 Abscesses at the injection sites developed in eight cases

APPENDIX CASE HISTORIES

Case 1. Male, aged 45 No previous skin disease, no family history of allergy

History

15.1.45 to 26.3.45 Neoarsphenamine 5.85 gm

14.5.45 to 23.7.45 Neoarsphenamine 5.85 gm

Condition on examination

27.8.45 Weeping eczema of right ankle Scattered areas of involvement on inner and outer aspects of left ankle, and to a less extent on left leg and right hand Both ankles showed well-marked petechiae (possibly related to tight bandaging)

3.9.45 to 7.9.45 Full course of BAL

Progress

16.9.45 Oozing on right ankle ceased, no oozing elsewhere

20.9.45 Desquamation of hands, forearms, legs, and ankles

29.9.45 Improvement maintained

7.10.45 Patchy areas of desquamation on forearms and ankles

Good improvement Discharged

Case 2 Male Labourer Impetigo at age of 12 Patient's mother suffered from asthma for five to six years before her death, one brother, aged 34, also asthmatic

History

12.6.46 Primary syphilis

12.6.46 to 16.6.46 Penicillin, 300,000 units

15.6.46 to 17.8.46 Neoarsphenamine 6.75 gm and bismuth 2.4 gm

17.8.46 Irritation of skin

28.8.46 Desquamation of trunk and limbs, fissures on hands

28.8.46 to 4.9.46 Daily injections calcium thiosulphate 5 cc

Condition on examination

4.9.46 Condition deteriorating Generalized desquamation with exfoliation of dorsum of right foot Fissuring of elbows, flexures of palms and fingers, and of back of neck Hands oedematous

5.9.46 Full course of BAL started

Progress

11.9.46 Improving No further desquamation, fissures drying up

18.9.46 Fissures healing well, though hands still oedematous

25.9.46 Skin normal except for slight dry cracks in palms of hands and soles of feet.

Case 3 Female, aged 38 Housewife No previous skin diseases, no family history of allergy

The dosage of dimercaptopropanol recommended in these cases is probably unnecessarily low. Eagle recommends a 10 per cent solution, and in severe cases gives six injections, on a body-weight basis, on the first two days, four on the third day, and two on the fourth, fifth, sixth, and seventh days. In several cases clinical evidence of relapse has occurred shortly after the end of the course of BAL. This has in every case responded satisfactorily to a further short course of injections, and we have not seen any instance of sensitization to the drug.

Cameron, Burgess, and Trenwith (1947) have studied the tolerance to BAL of rabbits with experimentally produced renal and hepatic damage. They have found that animals with renal damage differed in no way from normal controls in their response to large doses of BAL. When renal failure was complete or almost complete, the tolerance to BAL was lowered, but this was not pronounced. In the animals with hepatic damage, on the other hand, evidence of increased toxic symptoms was present, and some deaths occurred after doses of BAL well below the fatal level for normal animals. These authors have concluded that while care should be exercised in the administration of BAL to patients with impaired liver function, the presence of renal disease does not appear to be a contra-indication to its use. As might be expected in view of these results, neither in animals with normal renal function nor in the cases reported here or published elsewhere, has any evidence been obtained of damage to the kidneys specifically due to the administration of BAL.

Although in some of the cases described here it will be seen that pyrexia was present, there are no clear-cut indications associating any rise of temperature specifically with the injections of BAL.

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Summary

1 An account is given of 44 cases of arsenical dermatitis treated with 2-3-dimercaptopropanol (BAL), 41 of these cases were of the acute exfoliative type.

2 Three cases ended fatally, and in four more it was impossible to assess the

6 3 46 Hardly any exfoliation Except for branny desquamation in certain areas most of the skin was normal Many follicular pustules in the beard and pubic areas and on front of thighs and legs A large pressure sore over sacrum broke down and discharged pus, and later a large subcutaneous abscess in the left arm required incision and drainage

25 3 46 Folliculitis cleared completely with applications of 1 per cent aqueous crystal violet The skin generally has been normal for some days

Case 5 Male, aged 21 After four injections of an arsenical in 1943 generalized dermatitis which necessitated admission to hospital for 3½ months Skin clear when discharged

History

19 6 45 Given 0.05 gm Neoarsphenamine to determine whether hypersensitive On the same evening he felt hot, his face was flushed and showed some oedema under the eyes His skin generally felt irritable

Condition on examination

20 6 45 Admitted to hospital with generalized erythema, scrotum and penis most affected Pitting oedema of face Lassitude, anorexia, and nausea Temperature 99.6° F

21 6 45 to 24 6 45 BAL 2 c c twice daily

Progress

21 6 45 Slight vesiculation on interdigital areas of both hands

22 6 45 Groins and scrotum moist and oozing, with extensive hyperaemia extending up natal cleft Vesiculation starting on buttocks and between toes, bullous eruption on hands Temperature 101° F

23 6 45 Erythema fading on chest, otherwise no change

24 6 45 Little change, irritation less

25 6 45 Erythema fading rapidly Dry branny desquamation Groins drying and desquamating Temperature normal

26 6 45 Improvement continued

1 7 45 Relapse, moist dermatitis starting on outer sides of both thighs, extensor aspects of both forearms, and backs of both hands Two more injections of BAL given

2 7 45 to 4 7 45 Daily injections of BAL

3 7 45 Some improvement, skin less moist

9 7 45 Very marked improvement Keratotic skin of soles of feet now peeling No moist areas

12 7 45 Only heels and parts of soles still peeling

19 7 45 Skin normal Discharged

Scrapings of skin were examined for the presence of arsenic on the third day in hospital, but none was detected

Case 6 Female Housewife No previous skin diseases, no family history of allergy

History

5 1 45 to 8 3 45 Neoarsphenamine 3.9 gm on account of early secondary syphilis

10 3 45 Irritation and slight rash of both forearms

Condition on examination

12 3 45 Generalized erythema with some

History

9 10 44 Serum-positive syphilis Non-itchy papular rash developed four weeks previously

9 10 44 to 23 10 44 Arsphenamine diglucoside 1.65 gm Bismuth 0.6 gm
Rash almost clear after second injection Three days after third injection skin of face and neck became itchy and swollen, this gradually spread, the skin becoming erythematous

Condition on examination

10 11 44 Generalized erythrodermia, least marked on dorsa of hands and feet Marked subcutaneous infiltration Considerable scaling of forehead and neck, commencing also on trunk and limbs No oedema, fissuring, or oozing Temperature 100° F

10 11 44 to 14 11 44 BAL 2 c c daily, ascorbic acid 300 mg daily

Progress

Immediate rapid improvement noted for first two days, then more slow but steady progress

16 11 44 Many areas of normal skin appearing on arms, legs, and trunk Erythema and scaling of neck and lower lids

23 11 44 Skin clear except for neck and lower lids, where some improvement is apparent

17 12 44 Skin normal Discharged on 21 12 44

Clinical impression gained was that, although the case was not one of the most favourable for assessment, therapy with BAL caused a more rapid cure and easier convalescence Areas of completely healed skin appeared in six days

Case 4 Male, aged 29 Employed in engineering works, handling oils, greases, and 'white spirits' Skin had always been dry and 'irritable'

History

18 2 46 Admitted to hospital Acutely ill, temperature 103° F, with acute exudative erythrodermia affecting the whole of the body except the mid-portion of the trunk He admitted taking stovarsol for a number of weeks previously on account of intestinal worms He had apparently taken about 27 gm stovarsol, or 7 gm. arsenic Although he had had slight skin trouble for some weeks the generalized rash had appeared suddenly a few days before admission

Condition on examination

18 2 46 An intense generalized exudative and oedematous erythrodermia Frequent rigors Restless and agitated His mental confusion and incoherent speech suggested some cerebral irritation

On admission he was given three intravenous injections of 5 c c of 10 per cent sodium thiosulphate on alternate days His skin and mental state showed no improvement

26 2 46 to 3 3 46 Full course of BAL

Progress

27 2 46 Skin worse Erythema more intense, including now the part of the trunk previously spared Widespread oozing and crusting, but face less oedematous

2 3 46 Definite improvement Exudation largely finished, skin much paler and starting to peel

Condition on examination

24 8 44 Generalized maculo-erythematous rash with urticarial elements
24 8 44 to 27 8 44 BAL 2 c c twice daily

Progress

26 8 44 Erythema less intense Petechiae which had been present on backs of legs now very faint Less cutaneous oedema Some lesions resembling erythema multiforme on buttocks and a few papules in popliteal fossae
24 8 44 Skin normal except for staining of arms and calves of legs, and subsequently some desquamation of forearms and hands
5 9 44 Discharged

Case 9 Female

History

Secondary syphilis treated with semi-intensive course of Mapharside (1 265 gm) in Nov and Dec 1944
6 6 45 Penicillin therapy started
7 6 45 to 9 7 45 Neoarsphenamine 2 7 gm

Condition on examination

10 7 45 Marked dermatitis of legs and arms with severe itching
17 7 45 Scaling of neck, flexors of forearms, and adductor region of thighs
Marked hyperkeratosis of elbows Oedema of hands Nausea and headache
Apyrexia Full course of BAL started

Progress

20 7 45 Dermatitis clearing, irritation less
22 7 45 No itching Palms of hands oedematous and beginning to exfoliate, scaling on elbows less marked, front of forearms and inner side of thighs normal
30 7 45 Marked exfoliation of hands
8 8 45 Skin normal
Clinical impression gained was that this patient's rapid recovery was in response to BAL The spread of the dermatitis was checked sooner and the recovery was much more rapid than in a similar case not treated with BAL

Case 10 Male, aged 46 Worker with nitric acid No previous skin diseases, no family history of allergy

History

2 11 45 to 29 11 45 Stabilarisan 2 55 gm

Condition on examination

6 12 45 Typical early arsenical dermatitis which at this stage did not suggest that it would be severe Erythema and slight desquamation of face, neck, trunk, arms, forearms, and thighs Oedema of eye-lids, hands, and ankles
Treated with Lassar's paste and intravenous Calciostab
10 12 45 Full course of BAL started

Progress

19 12 45 Generalized exfoliation with oedema and weeping of neck, groins, and gluteal folds
Sixty injections of 40,000 units penicillin given on account of secondary infection with rise in temperature He improved gradually until 12 1 46,

for legs, which showed only a few small scattered patches of dermatitis
Oozing and desquamation of arms, groins, and neck

16 3 45 Condition was by this time much worse with increased oedema and serous discharge

Full course of BAL injections started

Progress

17 3 45 Slight improvement Oedema subsiding, but oozing still considerable Skin sprayed with penicillin and later treated with sulphathiazole ointment, as sepsis appeared to be developing

19 3 45 All lesions drier, oedema rapidly subsiding

22 3 45 Rather worse Painful nodules at injection sites in buttocks Sulphathiazole 20 gm given during next five days

23 3 45 Recurrence of oozing on left arm and forearm and both groins, with some fresh patches on both legs

26 3 45 All lesions improved again, and all dry except on the neck

28 3 45 Improvement maintained Abscess in right buttock incised, a week later the left buttock had also to be incised

31 3 45 All lesions dry.

21 4 45 Skin almost normal Discharged

Case 7. (Plate 5) Female, aged 42 No previous skin diseases, no family history of allergy

History

30 10 45 Secondary syphilis

31 10 45 to 17 12 45 Neoarsphenamine 1.95 gm and bismuth 0.8 gm

31 12 45 Papular rash on forearms of three days' duration

Condition on examination

4 1 46 Admitted to hospital with vesicular dermatitis of forearms and thighs, and erythema of arms, chest, and abdomen

11 1 46 Much worse Erythema now generalized Desquamation on trunk and limbs, and oozing on forearms, trunk, thighs, and legs

14 1 46 to 19 1 46 Full course of BAL

Progress

14 1 46 Desquamation marked, with commencing exfoliation on hands Slightly less oozing on forearms

18 1 46 General improvement, erythema less but desquamation still marked Oozing now confined to ankle region Some sepsis present on forearms and face, sulphathiazole ointment applied

23 1 46 Still improving No oozing Desquamation much less

2 2 46 Still generally improving

6 2 46 Slight erythema and pigmentation of trunk, with scaling on face and legs and slight scaling on groins

16 2 46 No erythema, scaling only on backs of heels

22 2 46 Skin almost normal Discharged

Case 8 Military Policeman No previous skin diseases

History

11 2 44 to 12 4 44 Neoarsphenamine 5.85 gm and bismuth 2 gm

24 5 44 to 26 7 44 Neoarsphenamine 4.2 gm and bismuth 2 gm

At the start of the second course of anti-syphilitic treatment forearms were erythematous

Progress

19 2 45 Oozing from ears ceased Desquamation of forehead and arms increased

21 2 45 Less itching Free desquamation on face, neck, arms, and chest Less oedema of arms

28 2 45 Skin normal except for desquamation of forehead, back of neck, and ears

Discharged

This case was not severe but was rather persistent and was not clearing up on the usual measures adopted

Clinical impression gained was that the result of therapy with BAL was very satisfactory

*Case 13 Male, aged 31**History*

5 12 43 to 9 2 44 Neoarsphenamine 5 85 gm and bismuth 2 gm

9 3 44 to 17 5 44 Neoarsphenamine 3 6 gm and bismuth 2 5 gm

14 6 44 to 22 6 44 Bismuth 0 4 gm

29 6 44 Neoarsphenamine 0 45 gm and bismuth 0 2 gm

Condition on examination

9 7 44 Admitted to hospital with generalized toxic erythema, urticarial wheals with purpuric areas on arms and legs His condition was thought to be the precursor of an acute exfoliative dermatitis

BAL 2 c c thrice daily injected for two days

Progress

Within 24 hours of the first injection the improvement in the skin condition was marked, although an urticarial element persisted till 25 7 44, when the patient was discharged There has been no recurrence

*Case 14 Female, aged 24 No previous skin diseases, no family history of allergy**History*

28 1 46 to 9 3 46 Neoarsphenamine 3 45 gm and bisoxyl 24 c c

1 2 46 to 6 2 46 Penicillin 1,280,000 units

6 3 46 Rash on arms

8 3 46 Erythrodermia of arms, abdomen, back, and face

9 3 46 to 12 3 46 Penicillin 1,240,000 units

13 3 46 Delivered of living male child

15 3 46 Exfoliation of whole body except palms and soles

Condition on examination

Generalized exfoliation, marked oedema of face, oozing and fissuring of neck, axillae, antecubital fossae, popliteal fossae, and buttocks No secondary infection Patient very ill Temperature 100° F Tongue red and sore

Liver enlarged to three fingers below costal margin

18 3 46 to 21 3 46 Injections of Thuostab 0 18 gm

23 3 46 No improvement Temperature 103° F

28 3 46 Full course of BAL started

Progress

1 4 46 Lesions much drier, oedema of face less, generalized dry exfoliation, no secondary infection Patient feels better Temperature 100° F

when he developed two large boils, one on the right forearm and the other on the left thigh, for which penicillin 100,000 units per diem was given for five days

21 1 46 Skin normal

Case 11 Female Housewife No previous skin diseases, no family history of allergy

History

1 9 43 Generalized secondary papular syphilide

1 9 43 to 28 7 44 Three full courses of Stabilarisan and Bismostab

20 9 44 Developed mild attack of jaundice, which cleared up in about six weeks

19 1 45 Commenced further course of Bismostab

27 3 45 Attended with moist eczema confined to chest, which was not at first thought to be arsenical

9 4 45 By this date it had developed into a generalized dermatitis

19 4 45 Admitted to hospital

Condition on examination

21 4 45 Generalized erythema with desquamation Fissuring on palms of hands and at corners of mouth, oozing of forehead and ears, oedema of eye-lids, ankles, and legs

22 4 45 Full course of BAL started

Progress

25 4 45 Fissuring on palms of hands much improved, oozing ceased, oedema of eye-lids, ankles, and legs less marked

15 5 45 Hair began to fall out

7 6 45 Has now lost greater part of hair from front half of scalp No itching or irritation Ready for discharge Although this was a very severe case she improved considerably from the time BAL was given, but her more recent progress was disappointing

In view of the eight months which elapsed between the end of arsenotherapy and the onset of skin lesions, it is uncertain whether the dermatitis was due solely to the arsenic or to the added effects of bismuth

Case 12 Female Chemical labourer at Imperial Chemical Industries (Dye-stuffs Division) Has handled many derivatives of aniline No previous skin diseases, no family history of allergy

History

11 12 44 to 26 1 45 Stabilarisan 3 75 gm

2 2 45 Slight early dermatitis

5 2 45 General erythema with slight desquamation on arms and face Patient complained of great irritation

15 2 45 Dermatitis worse in spite of treatment by calamine lotion, Lassar's paste, Calciostab, and calcium gluconate

16 2 45 Admitted to hospital

Condition on examination

17 2 45 Generalized erythema with areas of early desquamation Oozing on both ears Some oedema and marked exfoliation of flexor surfaces of both forearms, and over elbows

Full course of BAL started

on chest and limbs, face swollen, occasional delirium Temperature 102 to 103° F

29 10 44 Delirious Temperature 103 5° F

Rash almost disappeared on abdomen, face very oedematous, urine output much reduced

31 10 44 Comatose Urine output 350 c c in 24 hours, intravenous glucose saline started

1 11 44 Died

Post-mortem examination showed congestion of the lungs, and oedema with early bronchopneumonic consolidation of both lower lobes Kidneys pale and swollen, extensive necrotic changes in distal portions of tubules

Case 17 (Plate 6) Female, aged 22 Housewife No previous skin diseases, no family history of allergy

History

14 11 45 to 6 12 45 Neoarsphenamine 1 8 gm and Bismostab 3 c c

30 12 45 Complained of a few irritating spots on hands and feet

Treated with benzyl benzoate

1 1 46 Generalized papulo-erythematous rash affecting all areas except face, with oedema of hands, feet, and ankles Given calcium gluconate, ascorbic acid, and hesperidin daily Skin treated with 2 per cent phenol in calamine lotion until 14 1 46 Condition gradually deteriorating

Condition on examination

28 1 46 Generalized desquamative erythrodermia

Exfoliation of hands, forearms, legs, and feet Oozing behind ears, below eyes, and on hands and feet Fissuring of hands, fingers, feet, toes, and behind ears Skin of abdomen thick and rough Secondary infection under control Temperature 99° F

28 1 46 to 1 2 46 Full course of BAL

Progress

1 2 46 Condition better, no erythema of trunk and face, toes and soles of feet oozing slightly

14 2 46 During previous 10 days patient had relapsed and was showing a generalized erythema again with fine desquamation of chest, abdomen, face, and limbs, hands and feet exfoliating, ankles, shins, and soles oozing

14 2 46 to 19 2 46 Full course of daily injections of BAL

15 2 46 Very marked improvement, erythema totally disappeared

18 2 46 Arms and forearms almost normal Trunk completely normal, good improvement of legs, though slight oozing over right heel

25 2 46 Skin normal down to knees except for slight scaling of knuckles and right cheek

28 2 46 Skin normal except for roughening of knees, heels, and knuckles of left hand, slight crusting and desquamation over tibiae, fine scaling of scalp and of small area below left clavicle Scratch marks in left iliac fossa

Case 18 Female, aged 51 Housewife No previous skin diseases Hay-fever 25 years ago, paternal grandfather asthmatic

History

17 9 45 Started arsenical and bismuth therapy on account of gummatous ulcer on the pharynx

- 5 4 46 Skin much drier, large sloughs on buttocks where bisoxyl injections were given Temperature 102° F
 12 4 46 Skin very dry, marked exfoliation
 21 4 46 Skin of arms and trunk almost back to normal Face and scalp very scaly Temperature normal
 1 5 46 Condition of skin unchanged
 20 5 46 Complete loss of hair

Case 15 Male (Indian) aged 36 Ship's cook

History

- 23 2 46 to 16 3 46 Neoarsphenamine 2 18 gm and bismuth 0 8 gm
 20 3 46 Complained of itching skin Vitamin C 100 mg twice daily
 27 3 46 Admitted to hospital

Condition on examination

- Dry desquamating dermatitis of chest, arms, forearms, back, buttocks, thighs, and knees Moist exfoliation of neck, antecubital fossae, and forearms Face and back of neck weeping and crusted Blue line on gums
 29 3 46 Skin condition worse
 31 3 46 Fresh areas of oozing on lower dorsal and lumbar regions of back
 Full course of BAL started

Progress

- 3 4 46 Pyrexial Temperature 101° F
 4 4 46 to 11 4 46 Course of penicillin injections
 17 4 46 Skin condition now improved
 15 6 46 Now in very good health
 Clinical impression gained was that BAL had no influence on this patient

Case 16 Female, aged 24 No family history of allergy

History

- 21 9 44 Early secondary syphilis
 21 9 44 to 14 10 44 Neoarsphenamine 1 65 gm Thiostab given with each injection
 16 10 44 Burning erythematous rash on arms, neck, trunk, and legs, face swollen Cough with yellow sputum

Condition on examination

- 18 10 44 Admitted to hospital with generalized erythrodermia followed by desquamation and later exfoliation Some oozing from neck and chest, oedema of hands
 18 10 44 to 19 10 44 Crook's sulphur 5 c c intravenously daily
 20 10 44 to 22 10 44 BAL 2 c c twice daily

Progress

- 20 10 44 Face clear, diffuse macular itching rash on trunk and limbs, a little oozing on chest Temperature 99° F
 23 10 44 Temperature 100° F
 24 10 44 Slight oedema and desquamation of limbs
 25 10 44 Bad cough with thick-sputum Temperature 102 8° F Thick membrane on tonsils
 26 10 44 Throat very sore but less coughing No change in skin condition
 27 10 44 Rash clearing on abdomen, oedema on feet and hands, exfoliation

Condition on examination

Erythematous rash, papular and well marked on chest and abdomen, macular and slight on arms, legs, and face, early branny desquamation Very severe irritation, no vesiculation
 14 1 46 to 18 1 46 Full course of BAL

Progress

16 1 46 Feels well. Temperature normal Irritation and erythema less, desquamation more, particularly on limbs
 17 1 46 Marked improvement Desquamation has not extended and has nearly finished on affected areas Temperature 100 8° F
 18 1 46 BAL injections stopped because of rigor Temperature 104° F
 23 1 46 Condition seems to have improved, but there are some pustules on shoulder, desquamation continues on face and trunk
 25 1 46 Abscesses in both buttocks which were opened and evacuated of much pus
 28 1 46 Not much change in skin condition, pustules on back, shoulders, arms, and legs Some oozing of raw areas in flexures of knees
 6 2 46 Patient complains of sore throat and has follicular tonsillitis Temperature 102° F Number of small boils on shoulder, some pustules on back, paronychia infection of left ring finger Skin dry and slightly desquamating
 13 2 46 Abscess in right axilla and another in right buttock Skin seems otherwise satisfactory
 20 2 46 Many boils still present Skin has recovered well
 6 3 46 Skin normal Furuncles healing
 7 3 46 Discharged
 Readmitted 24 hours later with abscess in right axilla
 Discharged again after a few days

Case 21 Female, aged 42 Housewife Psoriasis for many years, no family history of allergy

History

26 11 45 Vaginal discharge Wassermann and Kahn reactions positive
 3 12 45 to 24 12 45 Neoarsphenamine 2 l gm and bismuth oxychloride 0 6 gm
 24 12 45 Generalized irritation of the skin which became progressively more severe
 27 12 45 Slight erythematous eruption
 7 1 46 Admitted to hospital with severe arsenical dermatitis Patient had had injections of calcium thiosulphate on 28, 29, and 31 12 45, and on 1 1 46 and 2 1 46

Condition on examination

Generalized erythematous rash with eczematous eruption on abdomen and legs, vesicular on feet and arms, with generalized desquamation Large oozing denuded areas of both arms and oedema of face, especially eyelids and legs She was a severe case, and it seemed likely that she would either die or have many weeks of disabling illness Penicillin cream and dressing applied to oozing areas Temperature 99 6° F
 9 1 46 to 14 1 46 Full course of BAL

9 11 45 After total of 5.25 gm neoarsphenamine and 28 c c bismuth oxychloride, generalized irritation of skin developed, 0.3 gm stabilarisan injected

Condition on examination

Generalized desquamation of back, feet, arms, legs, and soles of feet with erythema of chest, groins, buttocks, and backs of thighs Bismuth oxychloride 2 c c given

12 12 45 Admitted to hospital Irritation almost unbearable

Treated with calamine lotion externally Received seven injections of contramine, 2 c c on alternate days from 14 12 45 to 20 12 45 Abscesses at injection sites developed at end of course

Progress

The skin condition improved slightly up to 28 1 46, when it began to deteriorate

2 2 46 to 7 2 46. Daily injections of BAL into right thigh only, as no other normal skin was available After a few injections area became painful and remained so until the end of BAL injections

18 2 46 Erythema and desquamation decreased, irritation much improved by BAL

Case 19. Female

History

22 1 46. Admitted to hospital as a case of secondary syphilis with arsenical dermatitis Commenced anti-syphilitic treatment six weeks ago Three weeks ago developed irritating rash beginning on hands and extending to rest of body

Condition on examination

Scaly desquamating rash with underlying erythema of face, arms, and hands, much crusting with some oozing in two localized patches behind elbows, slight erythema on chest and back, legs almost clear Temperature 98° F

24 1 46 to 29 1 46 Full course of BAL

Progress

28 1 46 Considerable improvement in dermatitis, face almost clear Trunk clear, arms desquamating but improved, elbows dry, some desquamation and slight oozing in flexure of knees

30 1 46 Evidence of relapse, follicular eruptions on limbs and trunk Some pustule formation and exfoliation Slight weeping round ears and in flexures

6 2 46 Good progress Slight dryness and desquamation of skin

20 2 46 Practically full recovery

27 2 46 Skin normal except for slight residual branny desquamation on face and flexures of arms

Case 20 Female, aged 27

History

31 12 45 to 10 1 46 Stabilarisan 0.9 gm and bismuth 0.6 gm Before this she had received neoarsphenamine 1.35 gm (dates not stated)

11 1 46 Rash with very severe irritation

30343.

History

- 12 7 46 to 14 8 46 Neoarsphenamine 3.8 gm and bismuth 0.8 gm Penicillin ethyl oleate 2.4 mega units
 16 8 46 Irritation of skin of arms, with slight erythema of arms and legs
 23 8 46 Erythema much more severe
 24 8 46 Admitted to hospital One small moist patch in left antecubital fossa
 16 8 46 to 28 8 46 Calciostab 0.6 gm twice daily Vitamin C 500 mg daily
 28 8 46 Full course of BAL started

Condition on examination

- 29 8 46 Extensive weeping of neck, extremities, and trunk, particularly around genitals and adjacent surfaces of thighs Boracic lotion dressing applied locally

Progress

- 30 8 46 No improvement Face oedematous, especially infra-orbital areas Weeping areas now confluent and generalized
 1 9 46 Condition improved Moist areas on arms now dry
 2 9 46 Moist areas now restricted to upper and inner aspects of thighs Dry scaling over rest of body, with crusting on the chin Dry areas now treated with boracic ointment
 3 9 46 Oedema of face disappeared.
 7 9 46 Skin normal except for minute moist patches on upper and inner aspects of thighs
 8 9 46 Abscess of left buttock

*Case 25 Female, aged 46 Housewife**History*

- 4 2 46 Secondary syphilis treated with penicillin, neoarsphenamine (eight injections), and bismuth
 8 4 46 Erythema of both arms
 10 4 46 Admitted to hospital Skin lesions spreading, with oozing areas on arms and erythematous rash on thighs, legs, and forehead Calciostab administered intravenously, boracic lotion applied to oozing areas, and boracic ointment to erythematous areas
 11 4 46 Skin condition much worse, greater part of the body now involved, including abdomen, neck, and extremities Intense erythema, with oozing areas Full course of BAL started

Progress

- 13 4 46 Marked improvement of skin
 14 4 46 Purpuric lesions on both legs
 19 4 46 Skin condition worse, copious weeping of chest, back, extremities, face, neck, and head Pyrexia and bronchial catarrh Glucose was given intravenously twice daily, together with 1 c.c. liver extract intramuscularly Penicillin 30,000 units three-hourly
 21 4 46 General condition much improved, weeping largely ended
 22 4 46 Epileptiform attack two hours after receiving an injection of glucose
 24 4 46 Similar epileptiform attack
 25 4 46 Moist patches still present on legs, elsewhere skin dry and exfoliating.
 26 4 46 Skin condition much improved, but moist areas still present on neck and behind ears
 7 5 46 Discharged Skin normal, though oedema of the ankles still present

Progress

- 11.1.46 Obvious improvement, generalized erythema much reduced and desquamation appears to be more indolent. Denuded areas of arms and legs no longer oozing, though there are several patches of surface haemorrhage, no signs of surface infection, no irritation
- 16.1.46 Improving fast. Oedema of face gone but desquamation still present, condition of back returning to normal, abdomen and chest dry and scaling
- 23.1.46 Abscesses in both buttocks. Otherwise very much improved. Skin now dry except for a patch on left ankle
- 6.2.46 Skin very satisfactory, though still dry and scaling
- 13.2.46 Abscess on left breast
- 20.2.46 Skin becoming normal, though there is still dryness and branny desquamation in places
- 27.2.46 Skin fully recovered

Case 22 Male Working with oil for two years. No previous skin diseases, no family history of allergy

History

- 30.8.44 to 29.8.45 Neoarsphenamine 18 gm (three courses)
- 29.8.45 Dermatitis, appearing first at angles of mouth and steadily becoming worse

Condition on examination

- 5.10.45 Erythema, desquamation, and exfoliation of face, forearms, abdomen, groins, buttocks, and backs of thighs, oozing of right forearm and left groin, fissuring of palms of hands. Much irritation

Progress

Progress was slow and it was not considered that it was helped in any way by BAL (Dates of administration of BAL not given)

Case 23 Female Housewife. No previous skin diseases, no family history of allergy

History

- 2.10.45 Secondary syphilitic rash with anal condylomata
- 2.10.45 to 8.11.45 Neoarsphenamine 2.25 gm
- 24.11.45 Admitted to hospital

Condition on examination

Generalized erythema with desquamation and exfoliation on all areas. Oozing on front of neck, on upper third of flexor surface of left thigh, and in left popliteal fossa, secondary infection on soles and dorsum of toes of both feet, severe generalized excoriation. Temperature 101° F

- 25.11.45 Full course of BAL started, penicillin also given, 15,000 units three-hourly for seven days, and sodium thiosulphate 0.6 gm once daily for six days, together with local treatment to skin

Progress

Patient made a rapid and complete recovery and was discharged with a normal skin on 22.12.45, 29 days after commencement of BAL therapy

Case 24 Male Turner Impetigo of face in 1941 which developed into eczema of face and neck. No family history of allergy

- 19 6 46 Further improvement Trunk, arms, and legs dry, dead skin flaking off and showing healthy epidermis Face and lips still swollen, but ectropion less marked Movement of elbows and hands still limited owing to tension of skin Some fissuring of palms, with bleeding BAL injections completed
- 21 6 46 Further improvement maintained Face and hands less oedematous Hair beginning to fall
- 23 6 46 Elbows and hands now mobile, with only a few small cracks on the dry palms
- 25 6 46 Weeping present only on chin and behind ears Neck clear Oedema of face almost vanished Hands and face desquamating slightly No cracks on palms, movements of hands full and painless
- 27 6 46 Four toe-nails have dropped off, the new nails are already present Back now clear Chest and abdomen still desquamating slightly
- 29 6 46 Legs, abdomen, and back healthy and free of desquamation Slight desquamation still present on chest and arms, more marked on neck and face
- 3 7 46 All weeping ended Arms, trunk, and legs almost normal Face less scaly
- 6 7 46 Skin practically normal on face, and normal elsewhere
- 16 7 46 Discharged

Apart from BAL the other treatment used was

Sodium bicarbonate compresses on weeping flexures of arms for first two days after admission

Castellani's paint to weeping fissure behind right ear

Penicillin eye-drops

Olive oil rubbed over palms of hands on 19 6 46 and over face on 6 7 46

Penicillin was started on 3 7 46 for the luetic infection.

High protein diet throughout

Laboratory investigations

	Haemoglobin (%)	White cells (per c.mm.)	Eosinophils (%)	Plasma-proteins (gm per 100 c c)	Albumin (gm per 100 c c)
14 6 46	66	8,000	31	5.8	2.85
20 6 46				6.05	3.06
29 6 46	68	8,000	13		
5 7 46	88	9,000	5		..

Case 28 Female, aged 45 Housewife In childhood had 'eczema' each spring Patient states that if she rubs any liniment into the skin a rash develops No family history of allergy

History

13 12 44 Maculo-papular eruption on trunk, neck, and arms, peri-anal ulceration Wassermann reaction strongly positive

13 12 44 to 21 2 45 Sulphostab 5.7 gm and Chlorostab 2 gm

Condition on examination

9 3 45 Extensive dermatitis with purulent conjunctivitis of right eye Erythema of front of neck, under left breast, and on legs, desquamation of cheeks, back of neck, and back of arms, oozing from ears and eyelids, fissuring of hands and behind ears, where there was also secondary infection Calcium thiosulphate given

Case 26 Male, aged 25 Motor mechanic

History

25 3 46 Secondary syphilis Commenced arsenotherapy together with bismuth and penicillin

29 4 46 After the eighth arsenical injection patches of erythema developed on the arms Treated with calceostab 0.9 gm intravenously twice daily His condition responded initially to this treatment, but later relapsed

8 5 46 Admitted to hospital with widespread erythematous patches and some weeping areas Liver extract together with intravenous glucose administered daily Boracic lotion and ointment applied to the moist and erythematous areas respectively

10 5 46 Skin condition improved

17 5 46 Condition relapsed, skin being much more severely affected than it had been previously Full course of BAL started

Progress

24 5 46 Skin condition much improved, exfoliating freely

27 5 46 Occasional moist areas between thighs

1 6 46 Skin now dry, red, and scaly Patient still in hospital, due to abscess in buttock, which, it is claimed, can undoubtedly be attributed to faulty technique in the administration of penicillin which was given to counteract chest complications

Case 27 (Plates 7 to 9) Female, aged 21 No previous skin diseases, no family history of allergy

History

7 3 46 Primary, unhealed sore of right labium, Wassermann reaction positive

7 3 46 to 1 5 46 Stabilarisan 3.85 gm

24 5 46 Urticarial rash on arms and legs (which patient said occurred every summer)

25 5 46 Thiostab 0.45 gm Later that day eyes became swollen

She was not seen again by a doctor till 11 6 46, that is, two days before admission According to the patient the skin condition was at its worst at about 3 6 46, and since then had shown some improvement

Condition on examination

13 6 46 Admitted to hospital with severe generalized dermatitis Face grossly oedematous with weeping areas around ears, eyes, mouth, and front of neck Patchy desquamation of nose and face Hands oedematous with weeping fissures on palms, the skin of which was peeling off like a glove Upper part of trunk and thighs covered with fine scaling Red weeping dermatitis elsewhere, covered in places with dried yellowish-green serous exudate Skin between the toes loose and peeling Hands, forearms, feet, and legs grossly oedematous

Bilateral conjunctivitis with ectropion of both lower lids Temperature 97° F

Progress

14 6 46 Peeling complete on palms

Started full course of BAL injections

15 6 46 Skin unchanged General condition rather worse

17 6 46 Definite improvement Oedema of hands and legs less marked.

Case 31 Female, aged 34 Housewife No previous skin diseases, no family history of allergy

History

Treated for secondary syphilis since 1944, amount of arsenic received unknown

1 10 45 to 22 10 45 Stabilarisan 1 8 gm and Bisoxyl 4 c c

29 10 45 Acetylarsan 2 c c and Bisoxyl 1 c c

9 11 45 Patient defaulted Visited by Almoner, who was told by patient that on the day after the last injection she had developed an erythema which had been treated by her doctor

Condition on examination

9 11 45 Generalized erythema with severe itching and oedema of the face, especially of lips and eyes Weeping areas on both shins

10 11 45 Admitted to hospital Treated locally with powder and zinc oxide-boric acid ointment

13 11 45 to 16 11 45 BAL 2 c c twice daily

Progress

14 11 45 Oedema and itching less severe

19 11 45 Weeping ceased, erythema fading, some residual pigmentation, no more itching

23 11 45 Patient left hospital. Marked pigmentation of arms and legs, scaling of palms

14 12 45 No complaint, but some pigmentation still present Subsequently patient stated that an abscess developed on the buttock and was treated with heat

Case 32 Male, aged 61

History

Patient was a tabetic who had been bedridden for several years For psychological reasons he was undergoing treatment with Acetarsol After 40 tablets, he developed on 26 9 44 an acute dermatitis on the inner side of the arms and thighs and a follicular erythema on the trunk During the acute weeping stage boric acid compresses, and later zinc cream, had been applied

13 10 44 to 15 10 44 BAL 2 c c twice daily Zinc ointment locally and Soluseptasine ointment for the secondary infection

15 10 44 Erythema fading, secondary infection clearing up

20 10 44 Erythema completely faded, but skin thickened Bedsore over sacrum—treated with eusol and lotio rubra

30 10 44 Skin normal, bedsore healing

Case 33 Male An old tabetic who had previously developed dermatitis following tryparsamide This was treated with calciostab and cured after six injections of 0 9 gm

12 4 44 He started on a further course of tryparsamide After one injection he developed dermatitis and oedema of face, arms, and thorax This was treated with BAL 2 c c twice daily for four days The rash started to resolve after three days and most of the symptoms had disappeared by the seventh day

- 10 3 45 Admitted to hospital Daily injections of sodium thiosulphate given and calamine lotion applied locally
 15 3 45 to 18 3 45 Course of BAL injections

Progress

- 17 3 45 All areas of skin dry
 22 3 45 Skin normal except for desquamation of hands
 27 3 45 Abscess on left buttock at injection site
 12 4 45 Skin completely normal, and patient discharged

Case 29 Male, aged 29 Dermatitis (? scabies) in 1941 No family history of allergy

History

- 10.12 45 to 15.2 46 Received one course of arsenotherapy, together with bismuth
 12 2 46 Rash developed on scalp and gradually spread
 27 2 46 Admitted to hospital

Condition on examination

- 27 2 46 Scaling papular eruption on scalp, face, trunk, and limbs Desquamation of hands and feet Moist areas on neck, itching in groins and axillae
 18 3 46 to 23 3 46 Full course of BAL

Progress

- 22 3 46 All areas dry
 28 3 46 Very slight itching Ichthyol in Lassar's paste applied
 4 4 46 No itching
 16 4 46 Mottling on chest and abdomen only Fit for discharge

Case 30 Female, aged 43

History

- 3 9 45 Primary syphilis
 3 9 45 to 23 11 45 Mapharside 0.4 gm and Bisoxyl 10 c c
 28 1 46 to 11 2 46 Stabilarisan 2.25 gm and Bisoxyl 6 c c
 15 2 46 Erythema of both arms, zinc oxide lotion applied
 18 2 46 Erythema spreading to trunk and legs

Condition on examination

- 27 2 46 Generalized erythema, face oedematous with scaling, dermatitis of legs
 1 3 46 Admitted to hospital
 1 3 46 to 4 3 46 BAL 2 c c twice daily

Progress

- 4 3 46 BAL injections stopped Face more oedematous, legs oozing
 8 3 46 Oozing stopped, oedema subsiding
 18 3 46 Patient left hospital against advice Oozing had ceased, but the skin of the body and extremities was still scaly with some oedema of the legs
 1 4 46 Patient returned to clinic with weeping dermatitis of face, neck, arms, and legs Boil in left axilla and another on buttocks Treated with zinc cream and saline compresses
 12 4 46 Slowly improving, marked alopecia
 26 4 46 Skin practically normal, alopecia increasing, mostly on occiput
 6 5 46 Skin normal, alopecia unchanged

Condition on examination

Generalized exfoliative dermatitis, fissuring and oozing at flexures, gross infiltration and oedema of legs, arms, and face, abscesses in both buttocks and right axilla, patient acutely ill Full course of BAL

Progress

Oozing ceased on the ninth day after the start of the injections, and exfoliation and erythema on the 14th day The patient made a complete recovery

Case 37 Female Domestic work No previous skin diseases, no family history of allergy

History

Patient had received two previous courses of therapy with arsenic and bismuth

23 12 44 Neohalarsune 0.09 gm and bismuth 0.2 gm She had previously had injections bi-weekly After the fourth injection of her third course she developed a faint red rash of hands and feet which was diagnosed as scabies and treated as such

Condition on examination

25 12 44 Rash more pronounced, bright red erythematous blotches on hands and feet, spreading up forearms and ankles, remainder of skin clear

26 12 44 Admitted to hospital Rash as on 25 12 44, but with oedema on backs of hands, ankles, and eyelids Mild conjunctivitis BAL 2 c.c. injected

Progress

27 12 44 Rash subsiding on hands and feet, oedema unchanged, very faint erythematous rash now present over whole trunk and limbs BAL 2 c.c. injected

28 12 44 Rash on arms and legs definitely improved, oedema decreased, rash on trunk unchanged BAL 2 c.c. injected

29 12 44 Hands and feet normal, no oedema, rash on trunk and limbs almost imperceptible

31 12 44 General condition good, residual rash consists only of a very faint pink mottling of the back

1 1 45 Skin quite normal

Case 38 Male, aged 56 Motor driver

14 8 45 Admitted to hospital on account of generalized arsenical dermatitis
14 8 45 to 22 8 45 Full course of BAL

21 8 45 Skin worse on arms and face Temperature 102° F

23 8 45 Patient still pyrexial, general condition worse, though skin condition somewhat better Delirium at night with periods of mental confusion during the day Acriflavine emulsion applied at night

4 9 45 Condition unchanged Started on course of penicillin

7 9 45 Right gluteal abscess

The abscess slowly cleared up and the skin returned practically to normal except for a very fine desquamation The general condition became slowly worse, signs of uraemia developed, and the patient died on 19 9 45 Clinically it was considered that his skin condition had cleared up very much faster than a case of similar severity would have done if BAL had not been given

Case 34 Male, aged 20 No previous skin diseases, no family history of allergy

History

6 10 44 to 21 11 44 Stabilarisan 3.6 gm and bismuth oxychloride 14 gm
27 11 44 Rash on face, spreading down trunk Considerable oozing

Condition on examination

5 12 44 Generalized erythema with exfoliation on face, neck, shoulders, and chest, arms and legs desquamating Oozing from ears, oedema of eyelids with conjunctivitis and lachrymation Patient could only just open his eyes and mouth and had difficulty in speaking Temperature 100° F
6 12 44 to 11 12 44 Full course of BAL

Progress

11 12 44 No erythema on legs Exfoliation still present on neck and chin. Ears still oozing Temperature 98° F Blood-urea 184 mg per 100 c c
15 12 44 Ears have stopped oozing Slight exfoliation still present on neck and chin, with slight erythema remaining on trunk
21 12 44 Blood-urea 38 mg per 100 c c
23 12 44 Erythema vanished except for trace on trunk
29 12 44 Skin nearly normal, no erythema though slight desquamation still present
12 1 45 Eyes almost normal General condition good
17.1 45 Discharged

Case 35 Male, aged 32 Electrician's mate 'Dermatitis' of ears and face in June 1945 Treated with penicillin

History

2 9 46 Admitted to hospital on account of severe generalized dermatitis developing after the ninth injection of a course of arsenotherapy

Condition on examination

4 9 46 Severe generalized exfoliative dermatitis
4 9 46 to 6 9 46 BAL 2 c c twice daily

Progress

5 9 46 Condition worse
6 9 46 Feels better Generalized desquamation continues, but oozing has ceased
7 9 46 Skin peeling in large flakes
8 9 46 Indurated area in gluteal region at site of injection
9 9 46 Skin normal except for fissuring on palms of hands
13 9 46 Skin normal Abscess in right buttock
17 9 46 Abscess incised and drained
23 9 46 Discharged

Case 36 Female, aged 23 Married No previous skin diseases, no family history of allergy

History

7 3 46 to 15 4 46 Neoarsphenamine 3.3 gm and bismuth 1.1 gm
29 4 46 Slight irritation of backs of both arms Bismuth 0.2 gm
6 5 46 Admitted to hospital with severe generalized dermatitis

11 1 45 Further injections of BAL together with penicillin locally and intramuscularly

12 1 45 Patient died

Death was certified as 'resulting from toxæmia from widespread impetigo occurring in secondary syphilis, with exfoliative dermatitis due to intravenous N.A.B.'

Case 41 Male No previous skin diseases, no family history of allergy

History

8 10 44 Primary syphilis

10 10 44 to 28 10 44 Mapharside 1 14 gm

Condition on examination

29 10 44 Eczematization of hands and feet with early vesicle formation
Macular rash on the trunk with an underlying erythema

31 10 44 Rash fading

3 11 44 Further vesiculation beginning on both hands

5 11 44 Marked generalized lymphadenopathy, particularly in axillae and groins

7 11 44 Oedema of the ankles

10 11 44 Oozing vesicles of hands and feet Branny scaling

10 11 44 to 12 11 44 BAL 2 c c thrice daily

Progress

14 11 44 Exfoliation more marked, particularly on forearms and legs

17 11 44 to 21 11 44 Further course of BAL injections The skin continued to exfoliate until all the affected areas were shed, but there was no further eczematization or vesiculation

6 12 44 Skin practically normal, transferred to convalescent home

29 12 44 Skin normal, discharged

Case 42 Male, aged 39 General labourer Seborrhoeic tendency but no other skin diseases, no family history of allergy After two injections of the second course of antisyphilitic arsenotherapy, patient noticed a dry, scaly erythema on forehead and ears The eruption on the ears became vesicular, broke down, and became secondarily infected He was treated with rest in bed and bland applications He did well for about 10 days, when his condition degenerated rapidly into a generalized exfoliative dermatitis After the condition had been established for about two months he was given BAL, 2 c c twice daily for three days Improvement was noticed within 24 hours The skin began to dry up and within four days an entire new epithelium had formed He improved rapidly for about 10 days and then started to relapse, a further five injections were given Within a week the skin symptoms disappeared apart from some pigmentation

Case 43 Male

History

14 1 45 Primary syphilis

15 1 45 to 7 4 45 Stabilarisan 6 9 gm and bismuth 2 4 gm

23 4 45 Dryness of skin with some desquamation

7 5 45 Some oedema of right leg

14 5 45 Dryness, irritation, and desquamation on trunk and limbs

Case 39 Female No previous skin disease, no family history of allergy

History

11 4 46 Primary syphilis

8 5 46 to 3 7 46 Neoarsphenamine 3.8 gm and bismuth 1.6 gm

3 7 46 to 9 7 46 Six daily injections of penicillin, each of 500,000 units

24 7 46 Irritation of skin over lower abdomen and vulva

Condition on examination

31.7 46 Diffuse papular dermatitis of trunk and arms Dandruff of scalp with oozing eczematous area of occiput and back of neck

1 8 46 Admitted to hospital

1 8 46 Full course of BAL started, and 2 per cent ichthyol in boro-calamine applied to the skin

2 8 46 Scalp erythematous, scaling, and oozing Diffuse papulo-macular erythematous eruption of trunk, arms, and legs Scaling of dorsum of both feet

Progress

11 8 46 All signs of dermatitis disappeared except for weeping of scalp due to secondary infection

Case 40 Female, aged 31 No previous skin diseases, no family history of allergy

History

25 8 44 Secondary syphilis

19 9 44 to 21 11 44 Neoarsphenamine 2.4 gm

10 12 44 Presented herself at the treatment centre with much swelling of the face, impetiginous crusts on the scalp, and a mixed papular and pustular rash of the arms together with an erythema of the trunk She was admitted to hospital for further treatment

12 12 44 to 10 12 44 Neoarsphenamine 1.03 gm and Bismostab 3 c.c. The last injection was followed in 24 hours by the onset of dermatitis

Condition on examination

A severe exfoliative dermatitis, especially on the arms and legs, fissuring and oozing of neck, antecubital fossae, and wrists Some oedema of feet and lower limbs, dry cough

29 12 44 Full course of BAL begun

Progress

1 1 45 Considerable improvement in the general condition Oedema of feet disappeared, fissures showed signs of healing, and total area of normal skin was more extensive

3 1 45 The original bad prognosis revised, before BAL was commenced it was felt that a fatal termination was certain, but at the end of the course her ultimate recovery was considered probable

For the next three days condition remained stationary, but thereafter she became pyrexial and signs of a spreading secondary infection became more marked

8 1 45 Sulphonamide therapy begun Discontinued 24 hours later, owing to a reappearance of a generalized erythema

9 1 45 Oedema of the face reappeared and the general condition showed marked deterioration

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Condition on examination

15 6 45 Generalized exfoliative dermatitis, oedema of both legs and ankles
 Admitted to hospital
 20 6 45 to 25 6 45 Full course of BAL

Progress

10 7 45 No improvement. Course of sulphadiazine begun.
 1 8 45 Slight improvement, less oedema, erythema still marked
 17 8 45 Penicillin ointment commenced
 21 8 45 Penicillin ointment discontinued, no improvement Injections of
 thiosulphate also tried
 22 8 45 Slight improvement, slightly less exfoliation and oedema
 Clinically it was concluded that therapy with BAL had caused practically
 no improvement

*Case 41. Male No family history of allergy**History*

24 9 45 to 2 11 45 Stabilarisan 3 45 gm and bismuth 1 2 gm
 29 9 45 to 6 12 45 Penicillin 2,400,000 units
 9 11 45 Slight rash on arms
 26 11 45 Rash spreading, treated with calamine lotion

Condition on examination

1 12 45 Marked exfoliation over abdomen and upper part of thighs, des-
 quamation on arms and legs, no areas of erythema without co existing
 exfoliation Gross secondary infection under both arms, in groins, and
 upper lip Admitted to hospital
 5 12 45 Increased scaling of scalp
 8 12 45 No general treatment Infected area improving Some areas on
 thigh appear to be free of rash, general condition improved
 9 12 45 to 14 12 45 Full course of BAL

Progress

11 12 45. Exfoliation ceased
 20.12 45 Skin greatly improved
 24 12 45 Discharged

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Case 7 Condition 23 days later



Case 7 Condition at start of BAL therapy

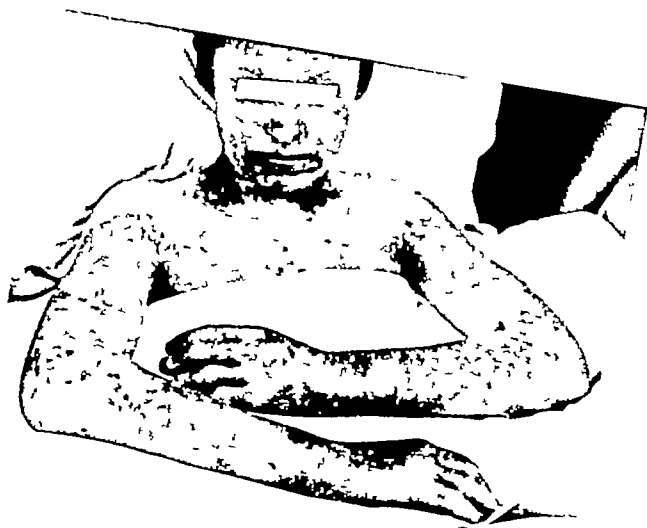


CORRIGENDUM

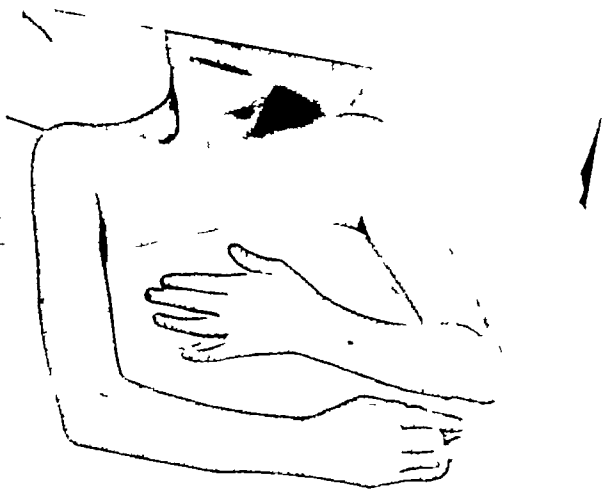
Proceedings of the Association of Physicians of Great Britain and
Ireland for 1947 (*Quart J Med* NS 16, 307)

In the report of the remarks made by Professor L J Davis the latter sentence should read as follows

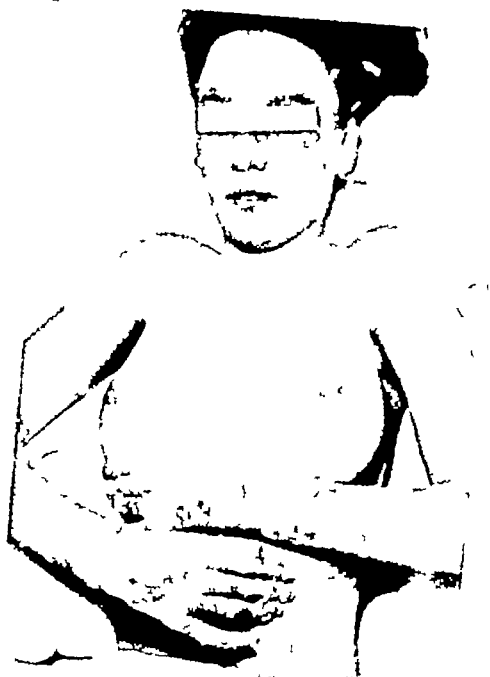
'Referring to the suggestion of a previous speaker that folic acid might be effective in preventing the neurological complications of pernicious anaemia if given in larger doses, he pointed out that with liver extracts, although intensive dosage was necessary for the treatment of neurological manifestations, it was unnecessary for their prevention, enough to control the anaemia prevented degeneration of the spinal cord'



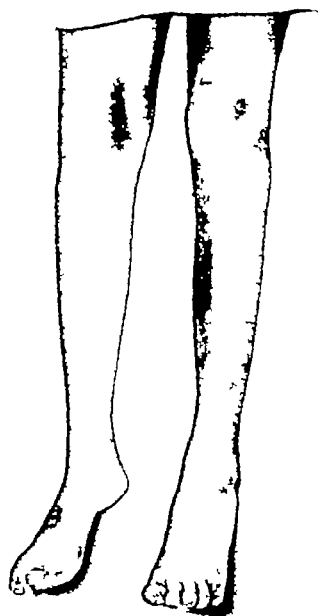
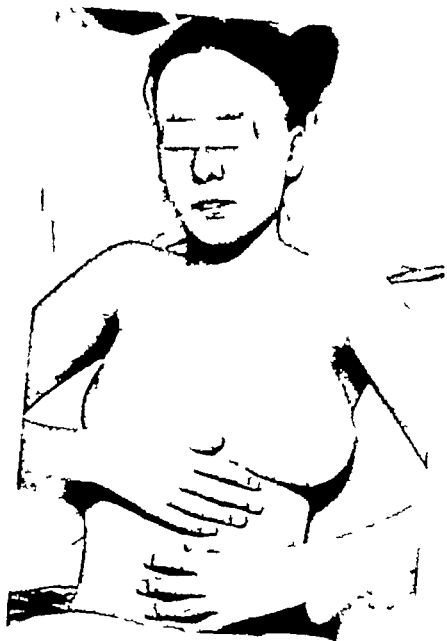
Case 27 Condition on day of commencement of BAL therapy



Case 27 Condition 14 days later



Case 17 Condition at start of BAL therapy



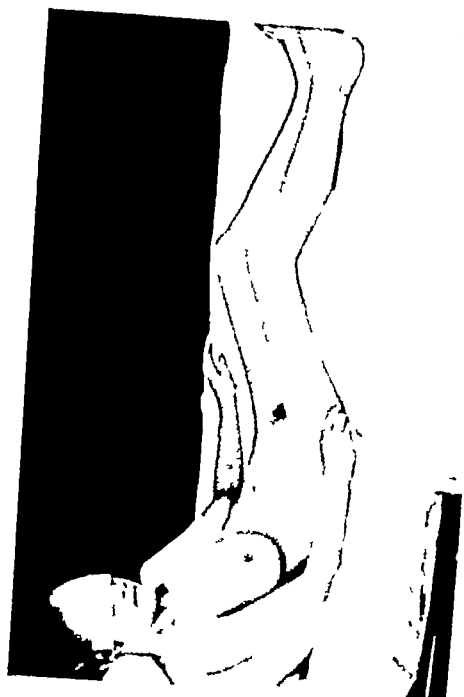
Case 17 Condition 22 days later



Case 27 Condition on day of commencement of BAL therapy



Case 27 14 days later



Case 27 Condition 14 days later



Case 27 Condition on day of commencement of BAL therapy

SEVERE HYPERTENSION IN YOUNG PERSONS

A STUDY OF 50 CASES¹

By ROBERT PLATT

(From the Department of Medicine, Manchester University)

DURING the course of an investigation into the heredity of hypertension (Platt, 1947) a careful differentiation had to be made between essential hypertension and hypertension secondary to other causes. It soon became apparent that hypertension in young persons nearly always belonged to the latter group, and that most cases of so-called malignant hypertension occurring at an early age were not examples of essential hypertension at all. Many accounts of hypertension fail to make this clear and give the erroneous impression that one of the outstanding features of malignant hypertension is its frequent occurrence in young adults and even in children. This is one of the reasons why malignant and benign hypertension have been regarded by some authors as separate diseases. Secondary hypertension is, of course, frequently of malignant type, showing papilloedema, high diastolic pressure, and rapid deterioration of renal function, but throughout the present paper it is assumed that the term malignant hypertension can only be properly applied to cases in which no primary renal or other cause for the hypertension can be found. It is the purpose of this paper to show that the conception of malignant hypertension as a disease commonly affecting young persons is fallacious, and it is its further purpose to discuss some of the causes of hypertension in young subjects.

Classification of Cases

The paper is based on the records of 191 cases of hypertension personally examined, to which have been added five cases of latent or chronic nephritis, Type I of Ellis (1942), in which hypertension was present. These cases form a consecutive and unselected series studied during the last 13 months. Unselected, that is, by ourselves (except that patients with diastolic pressures below 100 were not included), but in any such series there is a strong selection from outside, a 'pre-hospital deviation' in fact, for many practitioners will send cases of special interest to a unit engaged in the study of hypertension. There is no doubt that we have received far more than our fair share of hypertensive rarities, including a few which may well be described as museum pieces.

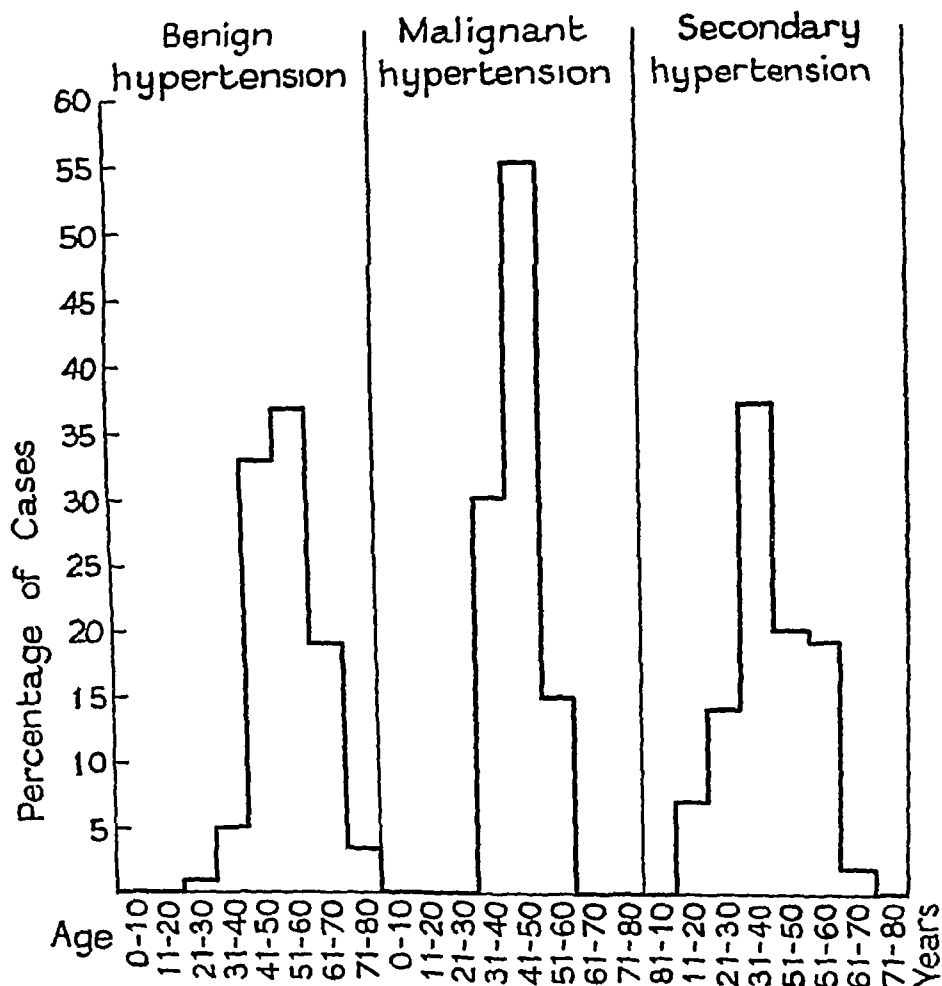
The distinction between essential and secondary hypertension is not always easy to make, for the finding of a urological abnormality does not prove its causative connexion with hypertension—for instance, a renal calculus in a

¹ Received August 10, 1947

evidence that secondary hypertension exists as a separate group from essential hypertension is furnished by the fact that there is no abnormal familial tendency to hypertension in the secondary cases (Platt, 1947)

Age Incidence of Hypertension

The Figure shows the age incidence in essential (benign and malignant) and secondary hypertension, and Table I shows that of 45 patients under the age of



40 years, 32 came into the secondary group. Only five of 24 patients under 35 years were diagnosed as essential hypertension. These figures do not include the five cases of chronic and latent nephritis, since nephritic hypertension, being well known to occur in young people, would unduly influence the age distribution. As a contrast to this, the distribution in patients of 40 years and over was essential hypertension 112 and secondary hypertension 34. The average

hypertensive subject For this reason the only practical clinical classification is to separate as essential hypertension (benign or malignant) all those in whom no cause for the hypertension can be found This means that there is no history of renal colic or 'bladder trouble', and that intravenous pyelography shows no urological disorder An intravenous pyelogram was made in every patient under 50 years of age in the present series, unless it was contra-indicated by gross renal insufficiency as revealed by urinary concentration tests and urea clearance It was also performed in all older patients if there was a history suggesting urological disease The distinction between malignant and benign (essential) hypertension was made on the presence or absence of papilloedema, although in many cases the diagnosis has been confirmed by autopsy, or by renal biopsy during sympathectomy This subdivision, of course, puts all cases into the secondary group if some possible cause for the hypertension is discovered No doubt some, especially amongst the older patients in this group, were really sufferers from essential hypertension, that is, they would have developed hypertension independently of the urological lesion found or presumed Even histological evidence cannot always make the diagnosis with certainty, for instance between atrophic pyelonephritis with hypertension and essential hypertension with pyelonephritis All that one can show is that in the vast majority of the younger cases, a possible cause for the hypertension exists Usually the aetiology is clear, for instance in polycystic kidney, recurrent pyelonephritis, pregnancy kidney, or polyarteritis nodosa, sometimes it is more difficult to prove, as in healed chronic pyelonephritis

It may be as well here to consider the evidence on which is based the opinion that numerous urological lesions may cause hypertension In some, the relationship is well established, for instance the kidneys of polycystic disease, chronic nephritis, and atrophic pyelonephritis (in typical cases) are anatomically and histologically distinct from those of essential hypertension Many renal lesions have become more firmly established as possible or occasional causes of hypertension since the possibility of unilateral renal disease causing hypertension became appreciated If hypertension is permanently cured by removal of a kidney, the evidence of a causal connexion is unequivocal Despite the attempts of Goldring and Chasis (1944) to discount most of the claims to cure by nephrectomy, it may be taken as firmly established that nephrectomy has resulted in the cure of hypertension in such diverse conditions as renal tuberculosis, tumours of the kidneys, infected hydronephrosis, infected calculus, pyelonephritis, aneurysm of the renal artery, and peri-renal fibrosis (Langley and Platt, 1947) If the unilateral existence of such abnormalities can cause hypertension, the presence of bilateral disease may obviously have the same effect The fact that nephrectomy has often been unsuccessful does not disprove the causal connexion, because it is often impossible to exclude bilateral disease, and because, as Wilson and Byrom (1941) have shown experimentally, sustained severe hypertension due in the first place to a unilateral lesion will cause secondary arteriolar changes which will affect the opposite kidney Operation undertaken when such changes have occurred must be foredoomed to failure Indirect

and double pelvis on the right, and one case with bilateral renal hypoplasia. Two of the unilateral cases also show congenital abnormalities.

Unilateral kidney disease One infected congenital hypoplastic kidney, three cases of hydronephrosis, one unilateral pyelonephritis with calculus, one case followed operation on a kidney for stone. Three cases of unilateral pyelonephritis with deformity shown by intravenous pyelogram.

Pyelonephritis In addition to the cases mentioned under unilateral disease, there were four cases of pyelonephritis established by the history together with urine culture or radiological abnormality or biopsy, and four cases presumed from a history of urinary infection.

Undiagnosed cases One girl of 19 years, with a history of swollen painful legs at the age of 10 years. One case of severe hypertension in a tuberculous subject, pyelograms showed both kidneys excreting and no evidence of renal tuberculosis, and there were pus cells in the urine but no organisms, urinary albumin 8 gm per litre, no oedema or other evidence of amyloid disease. The latter patient is to have a three-months pregnancy terminated and return for further investigation. (Autopsy later showed polyarteritis nodosa.)

Non-renal causes One typical case of Cushing's syndrome (age 25 years), a case of hyperostosis frontalis interna (Morgagni-Morel syndrome) aged 34 years, and a young man of 22 years showing neurofibromatosis of the sympathetic ganglia.

Four cases of special interest are briefly described in the Appendix.

In order of age, the cases under 35 years were as follows, the blood-pressure on admission is shown in each case.

Age 14	Pyelonephritis	Blood-pressure 245/150
„ 19	? Chronic nephritis (history of swelling of legs at age 10 years)	Blood-pressure 250/150
„ 21	Neurofibromatosis of sympathetic ganglia	Blood-pressure 235/130.
„ 22	Pyelonephritis	Blood-pressure 215/145
„ 23	Chronic pyelonephritis	Blood-pressure 170/115
„ 23	Undiagnosed	Blood-pressure 250/145 (later, polyarteritis nodosa)
„ 25	Cushing's syndrome	Blood-pressure 230/145
„ 26	Polyarteritis nodosa	Blood-pressure 215/160
„ 27	Benign hypertension	Blood-pressure 215/145
„ 28	Benign hypertension.	Blood-pressure 235/130
„ 28	Benign hypertension	Blood-pressure 195/120
„ 29	Hydronephrosis (right), double pelvis (left)	Blood-pressure 210/125
„ 30	Recurrent pyelonephritis	Blood-pressure 220/140
„ 30	Pyelonephritis	Blood-pressure 185/105
„ 31	Benign hypertension with Raynaud's syndrome	Blood-pressure 200/115
„ 31	Pyelonephritis (hypoplastic kidney)	Blood-pressure 205/130.
„ 31	Pyelonephritis and calculus	Blood-pressure 240/165
„ 31	Hydronephrosis	Blood-pressure 210/140.

ages are given in Table II. In each case 'age' means the age at which the patient was first seen in our Department.

TABLE I

		Number of Cases			
		Age under 35 years	Age under 40 years	Age over 40 years	Total
Essential	} Benign } Malignant Secondary hypertension	4	0	96	105
hypertension		1	4	16	20
		19	32	34	66
Total		24	46	146	191

TABLE II

	Average age (years)	Range (years)	Number of cases
Benign hypertension	53.2	27 to 73	105
Malignant hypertension	45.2	34 to 57	20
Secondary hypertension	39.5	14 to 61	66

Causes of Hypertension in Younger Patients

Analysing the causes of hypertension in 50 patients under the age of 40 years (including the nephritics), we find them divided into the following groups.

Essential hypertension Nine cases were diagnosed as benign hypertension. The youngest, 27 years of age, is rather an extraordinary case in which the possibility of secondary hypertension cannot be excluded, but the next youngest, aged 28 years, has had the diagnosis confirmed by renal biopsy during sympathectomy. The hypertension in this case was severe (235/130). The next, a woman of 31 years, has a relatively mild hypertension ranging from 200/115 to 145/95, which would probably not yet have been discovered had she not been a sufferer from Raynaud's syndrome. Another patient, a man of 35 years, has a blood-pressure which is still labile. Readings of 175/105 became normal during his stay in hospital. A fifth case is a woman of 36 years with gross obesity (18 stone). Four cases were diagnosed as malignant hypertension. In the youngest (aged 34 years) the diagnosis was confirmed by autopsy. Biopsy in another case showed benign hypertension histologically despite clinical papilloedema.

Chronic nephritis In four cases, a previous history of acute nephritis seemed to be clear. In another (aged 35 years) there was no history of an acute attack, but albuminuria is known to have preceded the onset of hypertensive symptoms by at least three years.

Pregnancy toxæmia In five cases there is a clear history of pregnancy toxæmia preceding the onset of hypertension.

Polyarteritis nodosa There were two cases. One (aged 26 years), confirmed at autopsy, is described in the Appendix. The other (aged 39 years) was diagnosed clinically, biopsy was suggestive but not definite.

Congenital abnormalities One case of polycystic kidney (with family history of Lindau's disease), one case with hydronephrotic double kidney on the left

benign hypertension do not complain of symptoms for many years after the commencement of their disease, it seems probable that benign and malignant hypertension have a similar age of onset

Some of the causes of hypertension in young persons are described.

APPENDIX

Case 1 Neurofibromatosis of sympathetic ganglia A soldier, aged 21 years, returned home on leave from Italy in November 1946 and was later admitted to hospital for impetigo. During examination, hypertension was discovered, the blood-pressure being 250/120, and he was transferred to my care on March 13, 1947. The man's intelligence was not high and it was only after careful questioning that a history of slight frontal headache and dyspnoea on exertion was elicited. This had apparently troubled him for about two years. It was also noted that he had had enuresis until the age of five years, and that he had always had some frequency of micturition. The mother (50 years), father (55 years), five older sisters, and two older brothers were all in good health. Examination showed bilateral papilloedema, with a macular exudate on the left side and some small exudates in the temporal field of the right retina. No cardiac enlargement or other clinical abnormalities were noted.

Intravenous pyelograms revealed a doubtful dilatation of the right renal pelvis and upper major calyx. A retrograde pyelogram, however, was considered to be normal. An X-ray of the chest was negative. The urea clearance was 79 per cent of average normal, the urine contained no albumin and cultures were sterile. The haemoglobin was 100 per cent and white cells 18,000 per c mm. A lumbar puncture showed a cerebrospinal fluid pressure of 170 mm of water and a normal fluid.

Depressor tests with pentothal and with tetraethylammonium bromide had comparatively little result, although there was some fall in both systolic and diastolic pressures, the pulse-pressure remained practically constant. In spite of this, he was transferred to the care of Professor A. M. Boyd for sympathectomy because the outlook otherwise seemed to be very unsatisfactory especially in view of the papilloedema. On May 10, a left lumbar sympathectomy and left transpleural splanchnic neurectomy was performed, the sympathetic chain from T4 to L4 being removed, and the greater splanchnic nerve resected. The sympathetic chain was seen to be expanded into jelly-like nodules at the ganglia, neurofibromatosis was suspected, and on re-examining the skin of the trunk with this in mind, a number of coffee-coloured areas were noted. On May 25, a similar operation was performed on the right side. The blood-pressure did not respond well to the sympathectomy and was still 190/110 on discharge. On July 21 the hypertension was no better with the patient lying (215/145), but on standing the pulse-rate rose from 72 to 124 and the blood-pressure fell to 155/95. It is too early to say what the eventual mean level will be.

I am indebted to Dr E. Pollak for the following pathological report.

'Left side. Histological examination confirms the diagnosis of Recklinghausen's disease (neurofibromatosis). The size of the ganglia is very much increased by hyperplasia of fibrous tissue of various types and increase of Schwann cells. These formations penetrate into the ganglia and are destroying nerve cells and fibres. Strands of nerve bundles are clearly recognizable but specific silver impregnations fail to show the existence of axons. The number of nerve cells inside the ganglia is greatly diminished.'

- Age 32 Pyelonephritis Blood-pressure 170/115.
 „ 32 Pyelonephritis (unilateral) Blood-pressure 245/155
 „ 33 Pregnancy kidney. Blood-pressure 200/140
 „ 34 Malignant hypertension Blood-pressure 250/140.
 „ 31. Hyperostosis frontalis Blood-pressure 170/125
 „ 34 Previous operation for calculus Blood-pressure 100/110

It is generally assumed that under the age of 35 years, chronic nephritis is the commonest cause of hypertension. Our experience is the reverse of this, since only five cases of chronic nephritis were observed during the time that these 24 cases of hypertension under 35 years of age were collected. This may have been due to selection, but if so it is surprising, since it is known that this Department is interested in kidney disease as well as hypertension. It is quite possible that many cases are wrongly diagnosed as chronic nephritis. Of these 32 cases of secondary hypertension (excluding the chronic nephritics) under the age of 40 years, 11 had papilloedema, which would distinguish them as hypertensives of the malignant type, and most of these would no doubt have been styled malignant hypertension by many authors. In the same age-group there were only four cases of malignant (essential) hypertension.

Finally, no survey of hypertension in young persons would be complete without reference to hypertension in children, which was uncommon in the present series. Probably the youngest case recorded is that of Marks, Thomas, and Warkany (1940), a girl of 10 months with obesity and hypertension (blood-pressure 200/110) due to an adrenal cortical tumour. Other authors have recorded severe hypertension due to unilateral renal disease at two and a half years (Semans, 1944), at five years (Howard, Forbes, and Lipscomb, 1940, Leadbetter and Burkland, 1938), six years (Powers and Murray, 1942), seven years (Kennedy, Barker, and Walters, 1941), and eight years (Platt, 1942). All these had systolic pressures of more than 200 mm. The author also saw a case of severe hypertension in a boy of 10 years, the cause of which was not discovered even at autopsy. Recent re-examination of histological material from the liver and kidney of this case strongly suggests *polyarteritis nodosa*.

Summary and Conclusions

1 Of 191 cases of severe hypertension (excluding chronic nephritis), there were 45 under the age of 40 years. Of these, only 13 appeared to be cases of essential hypertension.

2 No case of malignant hypertension under the age of 34 years was seen.

3 Young persons with the malignant type of hypertension are nearly always suffering from secondary hypertension, the underlying cause of which is often pyelonephritis, which may be on the background of a congenital abnormality. In such cases the disease may be unilateral.

4 When cases of secondary hypertension are carefully excluded the average ages for malignant and benign hypertension in the present series were 45.2 and 53.2 years respectively. Taking into account the likelihood that patients with

rapidly deteriorated and his blood-urea rose to 222 mg per 100 c c. Death on June 13, 1946, was due to renal and cardiac failure, the course being that of a rapidly progressive malignant hypertension.

Post-mortem examination showed the typical macroscopic appearances of polyarteritis nodosa. Small aneurysms, mostly filled with recent blood-clot, were found on the coronary, mesenteric, hepatic, and renal arteries, and elsewhere. A large thrombosed aneurysm of the cystic artery, 3.5 cm in length, was present and may have been related to the abdominal pain and tenderness. There was a smaller aneurysm 1 cm in diameter embedded in the liver substance, arising from a branch of the hepatic artery. I am indebted to Dr J. Davson for the following histological report:

'Aneurysms which had thrombosed and undergone partial organization were present in branches of the hepatic, coronary, pancreatic, mesenteric and renal arteries. In the spleen one artery showed almost complete fibroblastic obliteration of the lumen.

'*Kidney* Some glomeruli normal, many showed degrees of distortion and contraction, and adhesions were frequent. Tubules mainly dilated, some areas of atrophic tubules. Arterioles were free from arteriolosclerosis, and no necrotising arteriolitis was seen. Arcuate and smaller arteries showed pronounced endarteritis fibrosa in addition to a few organizing thrombosed aneurysms. The renal parenchymal changes are more probably due to the mainly healed peri-arteritis nodosa lesions of the arteries than to the hypertension, but the point cannot be settled with certainty.

'*Diagnosis* Periarteritis nodosa with aneurysm formation and partial healing.'

Comment A case of polyarteritis nodosa in which hypertension of the malignant type was an early and dominant feature of the disease.

Case 3 Hydronephrosis with secondary hypertension of malignant type A man, aged 31 years, was admitted to hospital on January 1, 1947, complaining of pain in the right lumbar region, haematuria, and headache. He had suffered from periodic severe headache, followed by vomiting, for about two years, the attacks coming every five or six weeks. There were no visual phenomena. The blood-pressure had not been taken and he had been treated for migraine. For five weeks he had had a dull aching pain in the right loin, and haematuria, and during this time there had been some frequency of micturition. Three days before admission he had noticed mistiness of vision. On inquiry he admitted that he had been losing weight and strength for about nine months and that he had noted shortness of breath on exertion. The family history was conspicuously free from hypertension, the two parents (aged 78 and 73 years) and nine elder siblings being alive and well. One brother had been killed in a motor accident. The patient looked pale and ill. The blood-pressure was 210/140. The fundi showed papilloedema and 'cotton-wool' exudates. The heart was enlarged and presystolic gallop was present. The abdomen was muscular and difficult to palpate. Neither kidney could be felt, but there was tenderness to the right of the umbilicus. Examination of the nervous system was negative.

An electrocardiogram showed left ventricular strain. The cerebrospinal fluid pressure was over 300 mm. Intravenous pyelograms showed no excretion. This was not surprising as the blood urea was 120 mg per 100 c c, and later 494 mg. Headache and vomiting continued, with cough and haemoptysis, and he died of cardiac and renal failure on January 14. Malignant hypertension was the provisional diagnosis, but it was made grudgingly in view of the negative family history, the age of the patient, and the pain in the loin. It was thought

remaining cells are pathologically affected. The whole architecture of the ganglia is, therefore, very much disturbed.

'Right side. As suggested by the macroscopic appearances, the histological examination does not reveal a condition identical with that of the left side. The ganglia, perhaps very slightly enlarged, do not show an extensive change of structure, but only some increase of connective tissue in some enlarged bundles of nerve fibres.'

Comment. Cases of von Recklinghausen's disease affecting the sympathetic nervous system have been recorded, but we have not been able to find an account of a case with hypertension. It is by no means certain that the hypertension in this case had any connexion with the disease of the sympathetic nervous system, especially in view of the history of frequency and enuresis, suggesting a possible renal cause, and in view of the lack of response to tetraethylammonium bromide and to sympathectomy. No biopsy of the kidney was obtained.

Six cases of von Recklinghausen's disease associated with chromaffin tumours of the adrenals have been described (Rosenthal and Willis, 1936), and it is possible that some such cause for the hypertension exists in this case.

Case 2. Polyarteritis nodosa. A soldier, aged 26 years, developed continuous frontal headache in February 1946 while in Belgium awaiting demobilization. This was followed by colicky pain in the right side of the abdomen. He stated that he felt a tender lump 'the size of a golf ball' in the right lumbar region. A few weeks later he noticed that his eyes ached and his vision became blurred, and about this time he had attacks of vomiting, specially in the mornings. The abdominal pain persisted. In the Army he had been involved in two motor accidents, but there was no previous history of illness of any importance. He had never been given a course of sulphonamide treatment. There was no family history of renal disease or hypertension. On April 25 he was admitted to hospital where hypertension was found (blood-pressure 200/150). There was bilateral papilloedema with exudates. There was some abdominal tenderness in the right hypochondrium, but no tumour. The heart was not enlarged. Examination of the nervous system was negative.

Investigations showed the following results: the Wassermann reaction was negative, red cells 4,440,000 per c mm, haemoglobin 80 per cent, white cells 9,800 per c mm, differential count normal, and blood sedimentation rate 26 mm in 1 hour. The cerebrospinal fluid pressure was 135 mm, and the fluid normal. The urine contained albumin (3 gm per litre), maximum specific gravity 1,006, cultures negative, no casts.

Urea clearance 60 per cent. Blood non-protein nitrogen 45 mg per 100 c c. Intravenous pyelograms, poor excretion right and left, no abnormality made out. Electrocardiogram normal.

A diagnosis of malignant hypertension was made and he was transferred to our care on May 13, 1946. Examination here confirmed the previous findings, but the blood-pressure was 215/160. The man looked pale and ill. Several points appeared to us to be against the diagnosis of malignant hypertension, the rarity of essential hypertension at this age, the absence of family history, the finding of a slight inconstant pyrexia, the abdominal pain, a leucocytosis on May 14 of 19,500 (polymorphs 81.5 per cent, eosinophils nil), some tender enlarged lymphnodes in the axillae and groins, and tenderness over the brachial and transverse cervical arteries. On this evidence a tentative diagnosis of polyarteritis nodosa was made and a lymphnode and a small piece of artery were removed for biopsy. The report on these was negative. The patient's condition

and the post-mortem was not performed until 24 hours after death. Microscopical examination of the kidneys was found to be useless owing to the extreme degree of post-mortem change. This is very unfortunate because if the diagnosis is correct, it is extremely rare for such a patient to live to the age of 39 years.

Comment. A case of uraemia in which neither chronic nephritis nor malignant hypertension seemed a really satisfactory clinical diagnosis. Post-mortem examination showed bilateral congenital hypoplastic kidney.

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ADDENDUM

Since writing this paper the author has seen another 14 cases. The details are as follows:

Age	Blood-pressure	Diagnosis
34	200/150	Malignant hypertension
33	260/170	Pheochromocytoma (no evidence of paroxysmal hypertension)
32	225/140	Uraemia, cause unknown
26	240/150	Undiagnosed (albuminuria discovered six years ago)
35	190/110	Essential hypertension
27	210/135	Pyelonephritis
34	260/170	Pyelonephritis
10	220/160	Chronic (Type 1) nephritis
37	180/110	Chronic (Type 1) nephritis
31	225/120	Unilateral pyelonephritis
38	200/105	Essential hypertension
26	180/115	Pregnancy toxæmia
17	210/140	Not yet investigated
25	245/140	Pregnancy toxæmia

Thus out of 64 cases under 40 years of age only 16 have been diagnosed as essential hypertension, and only five of these were malignant hypertension.

probable that a urological lesion would be found, but the patient was too ill for retrograde pyelography.

The post-mortem showed a large right hydronephrosis, and the changes of malignant hypertension in the left kidney, the perfect human counterpart of Wilson and Byrom's (1941) experiments. Microscopically the small amount of remaining renal tissue on the right side showed fibrotic glomeruli and atrophic tubules. On the left side there was lobulation of glomeruli with fibrinoid necrosis of afferent arterioles. Groups of tubules were dilated. Intralobular arteries showed endarteritis fibrosa. Other organs showed similar vascular changes.

Comment. A case of hypertension due to hydronephrosis, leading to a malignant termination. Presumably this could have been prevented by nephrectomy at an earlier stage.

Case 4. Bilateral congenital hypoplastic kidney. A man, aged 39 years, was admitted to hospital on March 22, 1947. About Christmas 1946 he began to vomit in the mornings. This continued, and since the end of January he had had headache lasting for a few hours nearly every day. General malaise had supervened, and dyspnoea on exertion. In February his urine was tested and albuminuria found. There had been no haematuria or oedema, and he thought that the urine had been more copious than formerly. There was no visual disturbance. There was no previous history of illness except pneumonia in 1942. In particular there had been no kidney or bladder trouble, and no frequency, dysuria, or oedema. His father was living and well at 80 years, his mother died of heart trouble at 60 years, and may, the patient thought, have had high blood-pressure. One sister aged 43 years was well. On examination the patient looked pale and ill. The blood-pressure was 220/130. There was slight blurring of the nasal edge of the optic disks and a small retinal haemorrhage on the right side. There was obvious narrowing and kinking of the arterioles. The heart was enlarged. There was no oedema.

Investigation showed a state of uraemia, the blood-urea being 320 mg per 100 c.c. on March 24. The urea clearance was 9 per cent. There was a severe anaemia, haemoglobin 56 per cent, red cells 3,193,000 per c.mm., and colour index 0.88, the white cells were 6,100 per c.mm. The urine showed from 1 to 4 gm. of albumin per litre (Esbach). The maximum specific gravity was 1.010. The cerebrospinal fluid pressure was 175 mm.

This man ran a slowly downhill course with drowsiness, anaemia, and epistaxis, and died on June 3. His last blood-urea was 460 mg per 100 c.c., and his haemoglobin 30 per cent. The blood-pressure tended to fall as he became more ill and anaemic. On May 29 it was 165/80. During life the diagnosis seemed to lie between chronic (Type 1) nephritis and malignant hypertension. Against the former was the absence of a history of acute nephritis, and yet the general clinical picture of anaemia and renal failure, with considerable albuminuria, and without gross papilloedema or raised cerebrospinal fluid pressure, suggested a nephritic rather than a primarily hypertensive disorder. It was therefore interesting to find that neither diagnosis was correct.

Post-mortem examination showed cardiac enlargement (450 gm.), pulmonary oedema, and hepatic congestion. The kidneys weighed 20 and 40 gm., the left being the larger. The capsules were adherent and the surface was coarsely granular, but with little or no scarring. There was no cortical pattern, the cortico-medullary demarcation was barely discernible, and the normal medullary markings were absent. The bladder, pelvis, and ureters appeared healthy.

The very small size of the kidneys in the absence of scarring was thought to represent congenital hypoplasia. The patient died during very hot weather,

THE SCHÖNLEIN-HENOCH SYNDROME (ANAPHYLACTOID PURPURA)¹

BY DOUGLAS GAIRDNER

(From the Department of Child Health, King's College,
University of Durham)

With Plates 10 to 13

Introduction

THE intention of this study is to clarify understanding of the group of conditions known variously as Schönlein's purpura, peliosis rheumatica, Henoch's purpura abdominalis, or anaphylactoid purpura. Answers have been particularly sought to the following questions. Is this group of conditions a definable entity? What is its pathology, pathogenesis, and aetiology? What is its relationship to nephritis, rheumatism, and polyarteritis nodosa? Material for study has been largely derived from patients seen personally, and reference has been made to the numerous case reports in the literature only so far as they are relevant to the questions studied. The scheme of the paper is as follows. Firstly, the condition to be studied is defined, and a name for it chosen. Next the history of the Schönlein-Henoch syndrome is outlined, emphasis being laid on those studies which have aided understanding of its aetiology. Thirdly, a clinical and pathological description of the condition is given, here special attention is paid to the lesions of the skin, a tissue amenable to study by biopsy. The relationship of the condition to nephritis and rheumatism and the roles of infection and allergy in its aetiology are considered. Finally, certain rare purpuric conditions are shown to be variants of the Schönlein-Henoch syndrome. The facts which have thus emerged are summarized and made the basis for a hypothesis of the aetiology of the Schönlein-Henoch syndrome which links it with nephritis, rheumatism, and polyarteritis nodosa, and thereby emphasizes the essential unity of this family of diseases.

Definition and nomenclature The condition which forms the basis of the present paper is identified by three main symptoms—an exanthem which will be shown to be specific and recognizable, gastro-intestinal symptoms (colic, vomiting, and haemorrhage from the gut), and joint symptoms (painful swellings of the joints). Haematuria is frequently also a feature. Finally, recurrences of one or more of this triad of symptoms are characteristic. The term Schönlein-Henoch syndrome is preferable to anaphylactoid purpura because purpura, as will be shown, is neither uniformly present clinically, nor is it the essential histological feature of the exanthem. Further, the eponymous term has more

¹ Received August 27, 1947

in some cases of angioneurotic oedema and of purpura . . . Before long the anaphylactic key will unlock the mystery of these cases'

The idea of anaphylaxis was independently applied to the problem of the purpuras by German writers Frank (1915) first used the term 'anaphylactoid' and Glanzmann (1916) developed the idea in more detail, though it was not made clear whether the term anaphylactoid implied a theory of the aetiology of this group of purpuric conditions (in which case the term 'anaphylactic purpura' would have been more logical) or whether it merely denoted that these cases bore a clinical resemblance, as Osler had pointed out, to the symptoms of serum sickness Glanzmann (1920) recognized that both infection and sensitization were involved, and described cases of 'post-infective anaphylactoid purpura' after otitis and scarlet fever The role of infection was not defined more closely and some later authorities (Cooley, 1945) have denied that infection plays any part In recent years Alexander and Eyermann (1927, 1929) have drawn attention to the possible aetiological role of food sensitivity Hypersensitivity to substances of both bacterial and non-bacterial origin has thus been suggested as the cause of the Schönlein-Henoch syndrome In the study of the present series of patients evidence has been sought for both types of hypersensitivity.

Material

The present series includes 12 patients suffering from the Schönlein-Henoch syndrome, all except one² of whom have been studied personally, either during the first illness or after recovery The main findings are set out in Table I

Age incidence Ten of the 12 patients were children between four and 15 years, two were adults of 40 and 48 years Previous authors have also found the condition to occur predominantly in childhood If the present series be combined with those of other authors (von Dusch and Hoche, 1890, Osler, 1895, 1900, 1904, Macalister, 1906, Glanzmann, 1916, 1920, Bartley and Bell, 1936), selecting from them such cases as can be certainly identified as suffering from the Schönlein-Henoch syndrome, a total of 58 cases in children of 14 years or below is obtained The incidence at the various ages is shown in Table II, from which it is seen that between three and 14 years of age there is a fairly constant incidence No cases of the Schönlein-Henoch syndrome have hitherto been described as such below the age of two years

Sex incidence Ten of the 12 patients in the present series were male Combining this with three larger series (von Dusch and Hoche, 1890, Macalister, 1906, Pratt, 1908) there are 85 male to 34 female cases In reading the literature one is even more struck with the heavier male incidence amongst cases which have developed some acute abdominal complication

Mode of onset There is a great variety in the mode of onset, and symptoms from any one of the three sites, skin, gut, or joints, may usher in the illness

² Case 10 was under the care of Dr V L Collins of the Central Middlesex Hospital, to whom I am greatly indebted for his notes

justification than many such, for Schönlein and Henoch, though not the first to describe isolated cases, were the first to describe them collectively

History of the Schönlein-Henoch syndrome The first and a most vivid description of a patient with this syndrome was made by an English physician, Robert Willan, in 1808, but the condition was not recognized as an entity until Schönlein in 1837 named the combination of joint symptoms with a rash *peliosis rheumatica* (πελιός = livid). His description includes a good account of the exanthem, emphasizing that it is composed of red macules distributed over the extremities and appearing in crops. The distinction from Werlhof's (1775) *morbus maculosus haemorrhagicus* (purpura haemorrhagica) is made on the absence of ecchymoses and bleeding from the mouth. Under aetiology a preceding cold is noted to be common. Finally Schönlein stated that 'If the exanthem is driven from the skin it may attack the internal organs, the heart and great vessels. Under such conditions a chronic inflammation occurs in these organs.' The syndrome attracted no further notice until Henoch (1874) reported a series of four cases in children, with a rash, colic, bloody diarrhoea, and painful joints. The rash was sometimes purpuric, at other times composed of red macules 'like those of an exanthem'. Thus both Schönlein and Henoch were aware that purpura was not an invariable feature of the rash. In later works Henoch (1899) emphasized the frequent association of nephritis, which might go on to anasarca and death. The differentiation of this group from Werlhof's purpura haemorrhagica was carried a step farther when Krauss (1883) showed that only in the latter were the blood platelets reduced. On the occasion of Henoch's 70th birthday in 1890 von Dusch and Hoche collected all the information then extant on the subject of *Die Henoch'sche Purpura*. In their collection of 44 cases from the literature, the largest we have, they gave a full description of the condition, including most of the important clinical facts. Osler evidently made the study of the Schönlein-Henoch syndrome and allied conditions a favourite medical hobby, for he returned often to the subject throughout the last 25 years of his life. In three papers (1895, 1900, 1904) he published a series of 29 cases, and summarized his ideas on the subject in 1914 in a final paper on 'The Visceral Lesions of Purpura and Allied Conditions'. Of his 29 cases, only 12 can from the data available be included within the Schönlein-Henoch group as here defined, for he included cases in which any skin rash was associated with any visceral symptom. Hence Osler's emphasis on the 'morphological inconstancy of the skin lesions' does not give an accurate picture of the exanthem of the Schönlein-Henoch syndrome. By calling attention to the analogies between serum disease and the Schönlein-Henoch group Osler (1914) did contribute an idea of lasting value.

'Chronic angioneurotic oedema, urticaria, and some forms of purpura are possibly anaphylactic phenomena in persons sensitised for certain protein substances. Phenomena of serum sickness reproduce in a graphic way the features of the skin diseases which the French group under erythema. The local oedema, the urticaria, the purpura, the arthritis, the vomiting and the persistence for years of the sensitiveness are paralleled by the life-long liability to recurrence

8	12 yrs F	None	(i) Rash (ii) Swelling of ankle and wrist	Arms, legs, buttocks, trunk, buccal mucosa, over 2 months	Colic at onset only	Swelling of wrists and ankles	Macroscopic haematuria and albuminuria	Recovery after 3 months; 1 year later well
9	12 yrs M	None	(i) Pain in foot (ii) Rash	Elbows, legs, buttocks, cheeks, prepuce, over 1 month	Colic, bloody diarrhoea	Puffiness of wrist	Albuminuria and microscopic haematuria	Well after 7 weeks, 3 months later after tonsillitis developed haema- turia, recovery
10	15 yrs M	Sore throat 10 days before	(i) Pain in knee (ii) Colic and vomiting	Arms, legs, over 1 week.	Colic, vomiting, blood in stools	Swelling and pain in knee	Albuminuria and microscopic haematuria at onset only	9 days after onset developed rheumatic carditis and left with mitral and aortic lesions
11	40 yrs M	'Influenza' 10 days before	Rash	Legs, arms, buttocks, over 1 year	None	Swelling of wrist	Albuminuria and microscopic haematuria at onset of attack of rheumatic fever only	Developed episode of acute rheu- matic polyarthritis; purpuric rash still recurring after 1 year Urine normal
12	48 yrs M	None definite; preceding 2 months malaise and loss of weight	Colic, vomiting, bloody diar- rhoea.	Arms, legs, buttocks, over 10 days	Colic, vomiting, bloody diar- rhoea	Swelling of knees and hands	Albuminuria and microscopic haematuria	Recovery after 5 weeks, but left with chronic nephritis.

TABLE I
Chief clinical findings in 12 cases of the Schönlein-Henoch syndrome

Case	Age Sex	Preceding infection	Symptoms at onset	Site of rash and duration	Gastro intestinal symptoms	Joint symptoms	Renal findings	Course and outcome
1	4 yrs M	(i) 1 month before, indolent sore on back (ii) 4 days before, coryza.	(i) Swelling of ankle (ii) Rash	Forearms, legs, buttocks, face, recurring over 2 months	Colic, vomiting, bloody stools	Swelling of ankle	Microscopic haematuria	Recurrences for 2 months, once precipitated by a tonsillitis. 10 months later well. Urine normal.
2	4½ yrs F	None	Rash.	Elbows, legs, buttocks, recurring throughout 3 months' illness	Colic, bloody diarrhoea.	None	Gross haematuria and albuminuria	Renal failure and death within 3 months. Autopsy showed sub-acute glomerulonephritis and cerebral necrotizing arteriolitis.
3	4½ yrs. M	None	Rash	Elbows, lower legs, recurring over 8 months	Colic, vomiting, bloody diarrhoea	Swelling of ankles and knees	Microscopic haematuria.	Recurrences for 8 months, thereafter well. Follow up 4 months later, urine normal
4	7 yrs M	None	(i) Colic (ii) Swelling of knee and ankle	Arms, shoulders, buttocks, legs, over 3 weeks.	Colic at onset only	Swelling of large joints of all limbs	None	Recovery after 6 weeks. Follow up 2½ years later, urine normal.
5	8 yrs M.	(i) 3½ weeks before, gastric influenza. (ii) 4 days before, second diphtheria immunization injection.	Vomiting	Elbows, legs, over 5 months	Colic, vomiting, bloody stools	Swelling of elbows, knees, ankles	Macroscopic haematuria for 5 months	Recovery after 5 months, but left with chronic nephritis.
6	9 yrs M	None	(i) Colic, vomiting, diarrhoea (ii) Haematuria	Arms, legs, over 2 months	Colic, vomiting, bloody stools	None	Gross haematuria	Two years after onset still subject to bouts of haematuria and exanthem; signs of latent nephritis
7	10 yrs M	Sore throat 2 weeks before	Painful knees and ankles	Arms, legs, buttocks, buccal mucosa, over 3 months	Colic	Swelling of knees and ankles	Transient albuminuria and microscopic haematuria	Recurrences over 3 months; 6 months later signs of latent nephritis

than the red macular exanthem, frankly haemorrhagic lesions were sometimes seen (Cases 2 and 9), varying from small petechiae to ecchymoses which occasionally went on to local gangrene (Case 2). Fresh skin lesions may be induced by a number of local procedures in patients in whom the condition is latent, as for instance between crops of exanthem. There is a striking delay of from 12 to 24 hours between the local manipulation and the appearance of the exanthem at the same site. Thus on firmly stroking the skin of a patient's arm with a blunt rod, the immediate wheal soon fades completely and next day its place is taken by a bright red line which subsequently undergoes the same slow fading to the brown colour already described. In the same way the skin-creases beneath a sphygmomanometer cuff become outlined on the day after a blood-pressure reading, and any intradermal injection produces a similar delayed reaction, which is therefore liable to cause a Mantoux or other intradermal test to be falsely read as positive. The rash of the Schönlein-Henoch syndrome is so characteristic that the diagnosis may be made on sight before the appearance of gut or joint symptoms.

(b) *Histology* The recognition of this exanthem as a clinical entity prompted an inquiry as to whether it possessed also a specific histology. In seven patients biopsies of the skin lesions were examined (Cases 2, 3, 5, 7, 9, 11, and 12) at the macular stage, either red or purple, in two cases (Cases 2 and 9) the very deep colour was characteristic of haemorrhage. The lesions varied in age from a day to a week, and in size from 0.5 to 1 cm. It was striking, therefore, to find essentially the same histological picture in all seven cases, the changes differing mainly in degree. The lesion common to all was an acute inflammatory exudate around the small vessels of the corium. The cells were polymorphs and histiocytes in roughly equal numbers, eosinophils were prominent in some (Cases 2, 3, and 9) and predominant in one (Case 11). Scattered red cells were generally seen in the neighbourhood of the perivascular inflammation, though always less numerous than leucocytes. In the neighbourhood of the larger infiltrations the collagen was swollen and stained poorly, but fibrinoid degeneration of collagen was not present. Although the process was largely confined to the corium, here and there it had spread to involve the epidermis, which was oedematous and infiltrated by polymorphs and eosinophils, while in one case (Case 5) collections of red cells formed minute bullae. The vessels of the corium were generally normal, but in one case (Case 11) showed endothelial swelling. Bacteria were never seen. In three patients skin biopsies taken at the same time from unaffected portions of the skin proved histologically normal. The few previous reports concern isolated cases (Silbermann, 1890, Osler, 1900, Heimild, 1943) and largely agree with the present findings. In a fatal case reported by Wassiheff (1937) the skin lesions were severe enough to have caused ulceration, the histology showed, in addition to cellular infiltration, marked changes in the vessels, which showed endothelial proliferation sufficient to cause obstruction, and medial necrosis of arterioles. An acute aseptic inflammatory reaction around the vessels of the corium, with frequently a tissue eosinophilia, thus forms the basis of the exanthem of the Schönlein-Henoch syndrome.

Reference to Table I shows that a rash, colic, or joint pains occurred as the first symptom with about equal frequency

The exanthem A rash was present in all 12 patients. The recurrent crops of skin lesions so characteristic of the condition have afforded many opportunities for watching their development (Plates 10 and 11, Figs 1 to 4), and for studying the histology of biopsy specimens (Plate 13, Figs 7 and 8)

(a) *Clinical* The first lesions are typically small urticae occurring discretely upon the extensor surfaces of the upper and lower limbs. At this stage they are

TABLE II

<i>Age in years</i>	<i>Number of cases</i>	<i>Age in years</i>	<i>Number of cases</i>
0-	0	8-	7
1-	0	9-	5
2-	2	10-	6
3-	5	11-	5
4-	7	12-	4
5-	2	13-	5
6-	2	14-	5
7-	3	—	—

somewhat itchy. Within a few hours they begin to change to pink maculopapules, becoming progressively less raised and darker in colour. By the following day they have become dusky red macules which do not fade on pressure. Their size is from 0.5 to 2 cm. in diameter, but some may coalesce to form larger patches. There is a slow regression from this stage, the red colour becoming more purple before fading to brown and finally disappearing altogether by the end of about two weeks. A similar series of events occurs at all affected sites, which are typically three—on the buttocks and lower back, around the backs of the elbows and extensor surfaces of the arms, and on the extensor surfaces of the lower leg, ankle, and foot. The cheeks, palms and soles, and prepuce are less often involved, while the trunk is generally spared. Small isolated red spots are to be seen occasionally in the buccal mucosa, but bleeding from the mouth and nose does not occur. The lesions are roughly symmetrical, but sometimes the rash is slightly more marked on one arm than the other. This has seemed to be the arm which was used the more, and was therefore generally the right arm (Plate 10, Fig. 2), but one patient in bed in a corner who tended to lean away from the wall on to his left arm showed an accentuation of the rash on *this arm*.

No mention has been made so far of purpura. The word *πορφύρα* means purple and has come to be used for any red or purple lesion which does not fade on pressure, and which is assumed to be due to haemorrhage. Although the earliest (urticarial) stage of the exanthem shows no sign of being haemorrhagic, in its later stages a haemorrhagic component is demonstrated by the brown staining of the skin which follows the macular stage. Since there is no evidence that this is due to melanin it must be due to haemosiderin, so that the red macules, which are the form of exanthem generally present when the disease is active, derive their colour and its persistence on pressure from haemorrhage. Less common

such cases is well established, we have less information on the histological appearances. In Silbermann's (1890) case, where a gastric perforation caused the death of a 10-year-old child, sections of the stomach showed thromboses with necrotic foci in stomach and small gut. Sutherland (1909) mentioned two cases, without details of the clinical illness, which came to autopsy, in the gut there were localized haemorrhages, with evidence of inflammation of some standing and collections of small round cells. Sturtevant and Graef (1933) reported the case of a man of 26 years, who developed the Schönlein-Henoch syndrome with symptoms suggesting peritonitis, laparotomy revealed a haemorrhagic extravasation into the wall of the terminal ileum. He died three days after operation. Autopsy showed numerous submucous haemorrhages, but serial sections failed to show any other changes. Wassilieff (1937) gave the autopsy findings in one case where in the stomach and intestine ulcers were found, near the necrotic edges of these ulcers the vessels showed fibrinoid necrosis of the media with leucocytic infiltration and endothelial proliferation, sometimes causing obstruction and thrombosis. These changes were analogous to those found in the skin lesions of the same case. The one case of the present series which came to autopsy (Case 2) showed scattered petechiae over the mucosal surfaces of the stomach, duodenum, and large gut, but unfortunately these lesions were not examined to discover whether their histology was analogous to the cutaneous lesions. From the scanty evidence available it seems that the more severe gut lesions of the Schönlein-Henoch syndrome show localized areas of inflammation and necrosis, and that the vessels in these areas may show endothelial proliferation, thrombosis, and fibrinoid necrosis. The histological descriptions are not detailed and eosinophilia is not mentioned, but the changes probably differ only in degree from the changes already described in the cutaneous lesions.

Joint symptoms occurred in 10 of the 12 patients, varying from transient puffiness of a single joint to recurrent painful swelling of many joints. The pain is rarely as severe as in the arthritis of rheumatic fever, nor is the joint so tender to touch or movement. Pain in a joint may be present without objective signs, while if any swelling is apparent it is generally due to a periarticular oedema. The impression was gained that these joint pains are not relieved by salicylates, though opportunities to observe this have been few. Fever, if present, is low-grade and rarely above 100° F. In all these ways the joint symptoms of Schönlein's 'peliosis rheumatica' differ from true rheumatic arthritis, a fact which has been pointed out frequently ever since Schönlein's use of the word 'rheumatic' to describe these cases.

Haematological findings This aspect of the subject has been fully investigated by numerous authors and there is general agreement that the blood picture shows no characteristic features (Bartley and Bell, 1936). In the present series the blood picture has been in conformity with the findings of others. The clotting time and bleeding time were normal in the four patients tested. Apart from a moderate polymorph leucocytosis, the white cells were normal and there was no increase in eosinophils, occasional cases have been reported with a

The question arises in what other skin conditions is such a histological picture to be found? Purpuric rashes from various causes have been studied. Biopsy specimens from two patients with thrombocytopenic purpura and from patients with aplastic anaemia, avitaminosis C, hypertension, and flea-bites showed only haemorrhages with occasionally small collections of lymphocytes in the neighbourhood of vessels, that is, there was no sign of an acute inflammatory process. In one patient with salyrgan poisoning, however, purpuric skin lesions showed, besides haemorrhages, some acute inflammatory reaction in the corium, there was no eosinophilia. Other conditions which bear some possible clinical resemblance to the exanthem of the Schönlein-Henoch syndrome include erythema nodosum, erythema multiforme, urticaria, and erythema annulare. Erythema nodosum has recently been studied by Dr S. A. Doxiadis in this Department and its accepted histology confirmed, the chief changes occur in the subcutaneous tissue rather than in the corium, with endophlebitis as the characteristic lesion. I have examined a biopsy specimen from a patient with erythema multiforme and have confirmed the text-book descriptions (Gans, 1925) of the condition, the chief features being oedema of the epidermis with vesiculation, oedema of the papillary layer of the corium, and a lymphocytic infiltration of the latter. In urticaria there is dilatation of the vessels of the corium with some lymphocytic infiltration (Carol and van Krieken, 1934). In none of these three conditions, therefore, is the picture that of an acute inflammatory reaction in the dermis as seen in the Schönlein-Henoch exanthem. Such a picture was, however, present in the single case of erythema annulare which has been studied (Carol and van Krieken, 1934), where the corium was infiltrated by polymorphs and some eosinophils, especially marked round the vessels, these appearances are similar to those found in the Schönlein-Henoch syndrome. It is noteworthy that it is to the exanthem of rheumatism that we have to go in order to discover a similar picture to that of the Schönlein-Henoch exanthem.

Gastro-intestinal symptoms were present in all except one of the present series. Of the 12 patients 11 had colic, eight had blood in the stools, and six had vomiting. The series sheds no fresh light upon this aspect of the syndrome, which has received considerable attention in the past. The abdominal symptoms mimic such surgical conditions as appendicitis and intussusception, and may also occasionally initiate the latter. Diagnostic puzzles result, especially when the exanthem does not appear until after the onset of abdominal symptoms, so that laparotomy has often been performed. A large number of reports of such cases were reviewed in 1930 by Bailey, and since then further reports have been made by Fraser (1930), Sturtevant and Graef (1933), Gray (1936), Althausen, Deamer, and Kerr (1937), Schwartzmann (1940), and Barnes and Duncan (1941). The findings at operation have generally been local oedema, often haemorrhagic, into the wall of the gut. The terminal ileum is the segment usually affected, although the whole small gut, caecum, and ascending colon have been involved in some cases. These local extravasations may lead to a variety of complications, such as obstruction, intussusception, or gangrene with perforation, which have occasionally proved fatal. Although the naked-eye appearances of the gut in

Schönlein-Henoch syndrome, gradual appearance of albumen and red cells in the urine, after sore throat a haemorrhagic nephritis, recovery

Case 9, aged 12 years, male The onset was with pain in one ankle, followed by a purpuric rash on the limbs, buttocks, and face Later he developed acute abdominal pain and was admitted to Hospital as a case of appendicitis The urine was then normal He continued to have crops of exanthem and colic with blood in the stools Albuminuria and microscopic haematuria gradually developed five weeks after the onset Four months after onset he had an acute tonsillitis, and the next day obvious haematuria with much albumen and many granular casts There was no hypertension. The blood-urea was 50 mg per 100 c c The urine cleared rapidly, and four months later was normal. After the nephritis there were no further crops of the exanthem

Schönlein-Henoch syndrome, left with a latent nephritis

Case 7, aged 10 years, male Two weeks after a sore throat he developed pains in the lower limbs which recurred intermittently for nine weeks, when an exanthem of Schönlein-Henoch type appeared over the backs of the arms (Plate 10, Fig 2) and the ankles At this time also the knees and ankles became swollen and he began to have attacks of abdominal colic The urine contained albumen and a few red cells on one occasion only Haemolytic streptococci were frequently demonstrated in throat swabs The symptoms recurred at irregular intervals over the next 10 weeks and then ceased Seen six months later he had remained well, but the urine contained albumen in small amount with microscopic haematuria The blood-pressure was normal Haemolytic streptococci were still present in throat swabs

Schönlein-Henoch syndrome, haematuria and nephritis, left with a chronic nephritis

Case 5, aged eight years, male The onset was with vomiting, blood in the stools, typical Schönlein-Henoch exanthem on limbs, and painful swollen joints The symptoms continued thus intermittently for five weeks when haematuria was added There was a mild degree of hypertension (130/100) throughout the following three and a half months' observation, macroscopic haematuria persisting After a streptococcal sore throat he developed some oedema of the hands and face four days later. Five months after the onset of the illness he still had macroscopic haematuria, hypertension, and a urea clearance of 38 per cent of normal, the exanthem was still recurring Seen six months later he had had no symptoms and the rash had disappeared Oedema of the face was present, the blood-pressure was much raised (145/118), the urine contained large amounts of albumen and sufficient blood to tinge the specimen The blood-urea was 76 mg per 100 c c (The haematuria persisting in the stage of chronic nephritis is notable)

Schönlein-Henoch syndrome, haematuria, proceeding rapidly to renal failure and death Autopsy showed subacute glomerulonephritis and cerebral necrotizing arteriolitis

Case 2, aged four and a half years, female The onset was with a rash on the legs After five days she developed colic and blood in the stools and was admitted three days later with a diagnosis of intussusception. The only finding then was albuminuria and microscopic haematuria, but next day the haematuria was gross, its appearance synchronizing with a fresh crop of a Schönlein-Henoch exanthem During the third week the urine became normal, but in the fourth week there was a recurrence of macroscopic haematuria She proceeded to develop steadily increasing oedema, hypertension, and hypoproteinaemia

marked eosinophilia (Vogel and Bassen, 1939, Hampton, 1941) The sternal marrow was examined in Case 11 and found to be normal, in Vogel and Bassen's (1939) case the sternal myelogram was also normal, apart from an eosinophilia. The fragility of the erythrocytes was normal in the single case examined (Case 11) The platelet count was always normal.

Capillary resistance and capillary microscopy The Göthlin tourniquet test for capillary resistance was applied in five patients during the active stage of the illness and during convalescence. Generally the capillary resistance is normal. In one patient (Case 11) the capillary resistance was always moderately decreased, saturation with ascorbic acid did not alter this, nor did it affect the 'orthostatic purpura' shown in this patient. This agrees with the experience of others with ascorbic acid in this condition (Lonberg, 1936, Jersild, 1938), though Böger and Schröder (1934) mentioned without details one patient whose symptoms were relieved by the exhibition of ascorbic acid. In Jersild's (1938) case both the impaired capillary resistance and the symptoms of the Schönlein-Henoch syndrome were relieved by prolonged administration of citrin, while in another case (Jelke, 1946) citrin was without effect. I have observed the patients' nail-bed capillaries with a microscope on a few occasions and have found a normal morphology, Macfarlane (1946) in three cases also found the capillaries normal, though Müller (1922) found dilated, elongated, and twisted capillaries in this type of purpura.

Nephritis and the Schönlein-Henoch syndrome Johnson in *Diseases of the Kidneys* (1852) referred to the association of purpura and nephritis. Henoch (1899) pointed out that nephritis was a frequent complication of the syndrome he described and might prove fatal, one of his three cases which developed nephritis went on to dropsy and death. Macalister (1906) listed 15 cases of Henoch's purpura from the records of Guy's Hospital, and concluded that this condition might 'be considered as a variety of Bright's disease and, therefore, the ultimate prognosis is usually unfavourable'. Osler (1914) emphasized that nephritis was the most serious complication in his patients, of whom seven died from renal failure. The results in the present series show that nephritis is indeed the most serious aspect of the condition. All except one patient showed some renal involvement either during the acute stage of the illness or after it, in four the haematuria was gross (and was then usually associated with blood casts and granular casts), and in the remaining seven patients the haematuria was microscopic. The subsequent history of these patients shows that the nephritis which is commonly associated with the syndrome may, like any other acute nephritis, go on either to recovery, to latent nephritis, to chronic nephritis, or to rapidly developing renal failure and death. Cases are recorded below which illustrate each of these outcomes. One prominent feature in these cases is that macroscopic haematuria often persists throughout all stages of a nephritis which follows the Schönlein-Henoch syndrome, so that a patient in the stage of a subacute or chronic nephritis may still have obvious haematuria. Apart from this feature the renal disease seems to differ in no way from the usual forms of Bright's disease.

and death, two developed chronic nephritis, and a further two patients remain in whom final recovery of the nephritis is in doubt. It will be seen that the outlook for the nephritis associated with the Schönlein-Henoch syndrome is serious.

The pathology of the renal lesion was studied in Case 2 of the series, whose clinical history was given previously (p. 105). The following is a summary of the renal changes found. Both kidneys showed advanced subacute glomerulonephritis (Type 1 nephritis of Ellis, 1942), in the intertubular tissues there were a number of foci with small haemorrhages and collections of polymorphs, eosinophils, lymphocytes, and plasma cells. These foci were reminiscent of the inflammatory foci seen in the skin in the cutaneous lesions of the same case. Search of the literature has revealed six further cases where the renal pathology has been studied (Watson and MacCallum, 1903, Goldhart, 1928, Sturtevant and Graef, 1933, Rathery and Dérot, 1934, Zothe, 1938, Johnson, 1942). In these seven cases where death occurred after the Schönlein-Henoch syndrome associated with a nephritis the mode of death was progressive anasarca in four (after illnesses of 3, 5, 7, and 9 months), intercurrent infection in one, abdominal operation (? peritonitis) in one, and not stated in one case. The renal lesion was subacute nephritis in three cases (in two of which there were in addition foci of acute inflammation), tubular nephrosis in one, chronic nephritis in one, and focal glomerular nephritis in one, no lesion was found in one case. Apart from our own case, the reports available scarcely allow a decision as to which of these cases were of Type 1 nephritis (Ellis, 1942), indicative of a post-infective origin. It may be concluded that the clinical course and pathology of the nephritis associated with the Schönlein-Henoch syndrome is not essentially different from the common forms of Bright's disease. There is, however, a special tendency to macroscopic haematuria at all stages of the nephritis, and such haematuria may continue over a long period of time without the development of hypertension or other signs of chronic nephritis, as was seen in Case 6, where there was recurrent haematuria over two years.

Rheumatic fever and the Schönlein-Henoch syndrome Reference has already been made to Schönlein's choice of the term *peliosis rheumatica* for the cases of purpura with joint symptoms, and his brief mention of the fact that the disease might 'attack the inner organs, the heart and large vessels'. When considering the joint symptoms it was pointed out that these have little in common clinically with the arthritic symptoms of rheumatic fever. In surveying the older accounts of 'purpura rheumatica' one is left in doubt as to whether this condition is or is not associated with rheumatic heart disease. For instance, Mackenzie (1898) in analysing 200 cases of purpura of various types from the London Hospital found 'in a considerable proportion valvular disease, usually mitral incompetence', while Macalister (1906) found 19 cases of purpura rheumatica in the records of Guy's Hospital, in five of which there was mitral stenosis. Endocarditis is frequently mentioned in older case records, but we may assume that, as in Mackenzie's cases, endocarditis or mitral incompetence was often diagnosed when no more than a systolic bruit was to be found. In other cases both endocarditis and purpura were probably part of a septicaemia, for in bacterial

The urine continued to contain large amounts of albumen and blood till the end. Fresh crops of exanthem appeared from time to time on the limbs. Her downhill course was marked by several convulsive episodes which were at the time thought to be due to hypertensive encephalopathy, though the blood-pressure was not raised during the fits above the previous level of about 180/135. Death occurred after a three months' illness with the child in coma and completely waterlogged.

Autopsy The kidneys showed advanced subacute glomerulonephritis and further details are given in a following section under pathology of the renal lesion. The heart was enlarged. In the brain, the left occipital lobe showed scattered haemorrhages up to 0.2 cm diameter. Histologically these were associated with striking changes in the arterioles of the meninges and superficial grey matter, showing necrotizing arteritis with hyalinization of the vessel wall and infiltration with cells, including eosinophils (Plate 13, Fig. 9).

Finally a Schönlein-Henoch type of rash, even in the absence of gastrointestinal or arthralgic symptoms, should always direct attention to the state of the kidneys, as the following case (not included in the 12 cases of the series) illustrates.

Schönlein-Henoch type of exanthem, three weeks later a severe nephritis with hypertensive encephalopathy, left with chronic nephritis

A girl, aged 14 years. One year previously she had had scarlet fever and seven months previously a septic hand. There had been no sore throats. The present illness began with recurrent crops of spots on the backs of the elbows and fronts of the ankles, which were red and itchy at first, turning later to darker red before becoming brown and fading. After three weeks of this skin trouble she developed haematuria and later oedema of the face and ankles. Examined at this stage of the illness she was found to have a rash which was beginning to fade. The lesions were brown macules which did not fade on pressure, about 0.5 cm diameter. Their distribution was on the extensor surfaces of the arms, specially round the backs of the elbows, on the buttocks, and on the fronts of the ankles. This picture combined with the description of the former appearance of the lesions in successive crops left no doubt that this was the Schönlein-Henoch type of exanthem (no biopsy was made). The patient also had an acute nephritis with large amounts of albumen and blood in her urine, hypertension (170/120), and generalized oedema. There was a conjunctival haemorrhage. The blood-urea was normal, and the serum-proteins 4.05 gm per 100 c.c. (albumen 2.05, globulin 2.00 gm per 100 c.c.). Next day she had a series of convulsions followed by coma. The blood-pressure was then 200/130, and cerebrospinal fluid pressure over 300 mm. Convulsions ceased after cerebrospinal fluid had been withdrawn. She was kept under observation for a further five weeks, during which time she lost her oedema, and the blood-pressure came down to 140/100. The exanthem did not recur. She was then transferred to another hospital and it was later learned that she had developed chronic nephritis.

The prognosis of the renal lesion can be gauged from the following facts. Of the 12 patients in the series one died in renal failure. Of the remaining 11 patients who were followed for periods up to two years, two had developed chronic nephritis (Cases 5 and 12), two had latent nephritis with albuminuria and microscopic haematuria (Cases 6 and 7), and the remaining seven patients had recovered fully. Out of 12 patients, therefore, one went on to renal failure.

which Glanzmann (1928) has applied the term 'orthostatic purpura' Eight months from the onset of the illness he developed an acute pharyngitis which his doctor described as 'typically streptococcal', although a throat swab was said not to have grown haemolytic streptococci He took to his bed for four days with the usual disappearance of the rash and the usual reappearance on returning to his feet Eighteen days after the acute pharyngitis he became suddenly ill with fever and very severe pains which flitted from joint to joint, with swelling and great tenderness of the affected joint The effect of salicylates was immediate, the acute symptoms responding within a few hours Thereafter he was left with a subacute arthritis of the shoulder, wrists, and finger-joints, and pain was liable to increase if salicylates were not taken The heart was normal, but over the next two months a soft mitral systolic murmur developed, there was no other cardiac abnormality and the electrocardiogram was normal The urine contained albumen and an occasional red cell at the stage of the acute polyarthritis, thereafter the only abnormality was an occasional red cell The joint pains cleared after two and a half months and the blood sedimentation-rate had by then returned to normal At the time of starting his convalescence there had been no further return of the rash since the onset of the polyarthritis, but as soon as he returned to his feet a fresh crop of exanthem appeared on the ankles

One other possibly pertinent fact appeared in the series, namely, that there was a family history of rheumatic fever in three patients (Cases 4, 5, and 7), the father in two cases and the maternal grandmother in another having suffered from this infection.

Infection and the Schönlein-Henoch syndrome Reference has already been made to the fact that some earlier authors, notably Schönlein (1837) himself and Glanzmann (1916, 1920), have stressed the fact that an infection often precedes the condition The pattern of the relationship between the infection and the Schönlein-Henoch syndrome has, however, never received attention, nor has any particular organism been held as chiefly responsible On the hypothesis that the condition was related to acute nephritis and rheumatic fever, both of which commonly follow a haemolytic streptococcal upper respiratory tract infection, evidence has been sought as to whether the Schönlein-Henoch syndrome is provoked by such infections

(a) *Infections preceding the first attack of the Schönlein-Henoch syndrome* Five out of 12 patients gave a history of some infection within one month of the onset These were Case 1, an indolent septic abrasion one month before and a coryza four days before, Case 5, 'gastric influenza' three weeks before (this boy had also received a second injection of diphtheria toxoid four days before; cf Jelke (1946)), Case 7, a feverish cold and sore throat two weeks before, Case 10, a sore throat 10 days before, and Case 11, 'influenza' 10 days before Thus in at least three of these five patients a preceding infection was definitely of the upper respiratory tract

(b) *Infections occurring in the course of the Schönlein-Henoch syndrome* The opportunity to watch the effect of a respiratory tract infection upon a patient showing this syndrome, or who had recently recovered therefrom, occurred on seven occasions in six of the patients

endocarditis the Schönlein-Henoch syndrome may occur, such cases being reported in the series of Macalister (1906) and Lippmann (1912) Osler (1914) stated that 'endocarditis occasionally occurs in very severe cases of what is called purpura rheumatica, but it must be very rare', and it is evident that he had never seen such a case, while Pratt (1908) in a series of 54 cases of the Schönlein-Henoch syndrome found none with endocarditis. It is frequently stated that in acute rheumatism purpura is rarely seen (Pratt, 1908), though Poynton (1911) mentioned five such cases, and Coburn (1931) found purpura in 11 out of 162 cases of rheumatic fever, but unfortunately insufficient details are given by these authors to enable us to decide whether the rash was of the Schönlein-Henoch type. A search of the literature has discovered only one previous case (Sturtevant and Graef, 1933) where rheumatic heart disease and the Schönlein-Henoch syndrome were clearly proved to be associated. In spite of the fact that most recent authors have been at pains to point out that the condition has nothing to do with true rheumatism, in two of our patients there was convincing demonstration that the two conditions may be closely associated.

Schönlein-Henoch syndrome after a sore throat in a rheumatic subject, nine days later rheumatic carditis

Case 10, aged 15 years, male. There was a history of his having had rheumatic fever at four years and 'several times' since, the heart having been always unaffected. Ten days after a sore throat he developed pain in the knee, colic, and vomiting. After three days he was admitted to the surgical ward of a hospital. He was then found to have a Schönlein-Henoch type of exanthem, partly macular and partly purpuric. The stools contained blood. The urine contained albumen and a large number of red cells. The heart was normal. He continued to have colic with bloody stools and crops of fresh skin lesions for a further five days, when a mitral systolic murmur was first heard. On the following day he developed pain in a shoulder and knee-joint and a mitral diastolic murmur was heard. The patient went on to develop a typical rheumatic carditis and was left with an enlarged heart, mitral stenosis, and aortic insufficiency. Followed for a further two and a half years he has had no further acute episodes. The urine has remained clear apart from the initial haematuria.

History of two attacks of rheumatism, Schönlein-Henoch type of exanthem recurring over six months, after a sore throat, further attack of rheumatic polyarthritis

Case 11, aged 40 years, male. At the age of 24 years and again at 32 years he had had short attacks of 'rheumatism'. Ten days after a febrile illness of three days' duration, diagnosed as influenza, he developed swellings on both legs and a rash on the legs and buttocks, later also on the backs of hands and forearms. The wrists were swollen. On taking to his bed these symptoms disappeared, but as soon as he got up the symptoms recurred, particularly the rash and swelling on the legs and ankles. He continued thus for four months. Examined at this stage he was found to have the Schönlein-Henoch type of exanthem, partly purpuric and partly macular over the shins, buttocks, forearms, and backs of the hands. The biopsy picture conformed to the histological picture already described. There was a chronic purulent tonsillitis, from which a heavy growth of haemolytic streptococci was obtained. A full course of intramuscular penicillin followed by tonsillectomy failed to prevent the reappearance of the rash on his shins and ankles whenever he attempted to get up, a condition to

the patients harbour haemolytic streptococci in their throats. These facts suggest that infections, particularly streptococcal respiratory infections, play a dominant aetiological role in many cases of the syndrome.

Allergy and the Schönlein-Henoch syndrome The incidence of allergic illness (asthma, hay fever, or eczema) amongst the families of the present series of patients was insignificant. None of the patients had had allergic illnesses themselves. Bartley and Bell (1936) also found no undue incidence of allergy amongst their cases, though Seidlmayer (1939) found a significant incidence of allergic illness amongst the families of his cases. The question must be left open. There is, however, evidence that the syndrome may occasionally be caused by sensitivity to a food, although none of the cases of our series appeared to be so caused. Alexander and Eyer mann (1927, 1929) published a series of 10 cases in which purpura or urticaria and abdominal symptoms were provoked by various foods to which the patient had become sensitized. Similar cases were later described by Kahn (1929), Barthelme (1930), Diamond (1936), and Hampton (1941). The allergens responsible in these cases included milk, egg, plums, pork, onions, and wheat. These allergens were indicted sometimes from the patients' history and sometimes by dietetic tests. Confirmation was obtained by withholding or giving the suspected food and noting whether symptoms followed, or in a case of Hampton's (1941) by observing colonic spasm fluoroscopically. Skin tests were usually unhelpful. In the majority of the 16 cases described by the above authors, purpura and abdominal colic were the only symptoms, and joint symptoms, blood in the stools, and nephritis occurred less often than in the general run of cases. Nor is the description of the rash generally detailed enough for one to judge whether or not it corresponds to the Schönlein-Henoch type of exanthem. Only four of the 16 cases were children, and the sex ratio was 11 female to 5 male subjects. In all these ways therefore the cases reported as examples of the syndrome resulting from food sensitivity tend to differ from the usual Schönlein-Henoch syndrome. Nevertheless a recent case report (Brown, 1946) furnishes more convincing evidence that the full syndrome along with haematuria and nephritis may be provoked by food sensitivity.

Schönlein-Henoch syndrome induced by sensitivity to tomatoes, laparotomy, left with latent nephritis

A nine-year-old boy was seized with an attack of colic, bloody diarrhoea, vomiting, and stiffness of a hip joint. He then had a purpuric rash on the trunk, but during subsequent recurrences the purpura was particularly round the elbows. He was admitted to hospital as a surgical emergency. Laparotomy disclosed only congestion of the terminal 18 inches of the ileum with enlargement of the mesenteric lymphnodes. Three days later he had a recurrence of his original symptoms and in addition there was an itchy swelling of the face and neck, and haematuria, further recurrences continuing at intervals over the next four months. The blood findings were normal. It was noticed that symptoms came on two hours after eating tomatoes, and that ingestion of small amounts of this food was followed by urticaria, purpura, melaena, and haematuria. Tomato pulp gave a strongly positive skin reaction. He remained free of symptoms so long as he ate no tomato, but the urine continued to contain red cells and casts.

Case 1 While at home after his first attack of the syndrome, he developed acute tonsillitis. Next day he had a fresh crop of the exanthem. Two months later he passed through a pneumonia without incident.

Case 3 While in hospital with the syndrome, recovering from a recent attack of the syndrome, he developed fever and cervical adenitis. The throat was not sore, but a swab from it grew haemolytic streptococci. The urine, which had previously contained no albumen and only an occasional red cell microscopically, on the day after the fever contained macroscopic blood which persisted for four days. Seven days after the fever there was a fresh crop of exanthem.

Case 5 While in hospital with the syndrome he developed an acute tonsillitis, from which a throat swab grew haemolytic streptococci. Synchronously there appeared a fleeting scarlatiniform erythema on the trunk. Four days later there was a fresh crop of the exanthem. Seven days after the tonsillitis, oedema of the hands appeared for the first time.

Case 7 While in hospital with the syndrome he developed an afebrile coryza without sore throat. A throat swab was negative for haemolytic streptococci. There was no effect upon the course of his illness.

Case 9 While at home convalescent from a series of bouts of the syndrome he developed acute tonsillitis. A throat swab grew haemolytic streptococci. One day later gross haematuria occurred (previously he had had only microscopic haematuria).

Case 11 While at home convalescent from the syndrome, the exanthem of which had persisted for six months, he developed acute pharyngitis. A throat swab was negative for haemolytic streptococci. Eighteen days later he developed rheumatic fever.

Thus in five patients in whom there occurred an acute febrile upper respiratory tract infection, this was followed in four by an exacerbation of one or more symptoms within one to seven days and in the fifth by an attack of rheumatic fever 18 days later. In four of these patients a throat swab was examined and in three grew haemolytic streptococci. By contrast an afebrile coryza and a pneumonia provoked no exacerbation or relapses. From this small series we may conclude that haemolytic streptococcal infections of the upper respiratory tract tend to provoke relapses or exacerbations of the syndrome.

(c) *Haemolytic streptococcus carriers and the Schönlein-Henoch syndrome*
When sought, this organism was present in the throats of the majority of patients who had, or had recently had, the condition. In five patients (Cases 3, 5, 7, 9, and 11) it was present on two or more occasions and in one (Case 12) was absent. The organism was present in the absence of sore throat, often on many occasions, as well as in one patient (Case 11) who had a chronic purulent tonsillitis. A control series of 10 patients in the same wards suffering from a variety of conditions gave only one throat swab positive for haemolytic streptococcus. Since the present paper was completed six further patients with the syndrome have been seen, all children, four had signs of a recent tonsillitis and all six had haemolytic streptococci present in the throat. To summarize, a sore throat often precedes the onset of the Schönlein-Henoch syndrome, subsequent streptococcal infections generally provoke relapses or exacerbations, and a large proportion of

the patients harbour haemolytic streptococci in their throats. These facts suggest that infections, particularly streptococcal respiratory infections, play a dominant aetiological role in many cases of the syndrome.

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It may be concluded that sensitization to non-bacterial products may provoke a Schönlein-Henoch syndrome precisely similar to that which follows infection

The Schönlein-Henoch syndrome in infancy In discussing the age incidence it was stated that the syndrome rarely occurs below the age of four years, and has not been reported below the age of two years. This is true if the triad of symptoms, in the skin, gut, and joints, is taken to comprise the syndrome. There is, however, a condition which occurs in later infancy which, it is suggested, is the form of the Schönlein-Henoch syndrome which is manifested at this age. The following case illustrates this contention

Case 13 Tonsillitis and otitis media, 10 days later painful swellings of both legs, with Schönlein-Henoch type of exanthem

A male child, aged 16 months. There was a striking family history of rheumatic fever, two maternal and one paternal siblings having suffered from this, in one case fatally. Ten days after a tonsillitis and otitis media one ankle became red, swollen, and very tender. Next day both legs were swollen and tender, and a rash appeared. Examined at this stage the temperature was 102° F. The left ear-drum was perforated and discharging pus. Both legs from ankle to thigh were much swollen with a brawny oedema, and were very painful to touch or movement. There was a florid eruption on the cheeks and the backs of the arms (Plate 12, Figs 5 and 6), and scantier lesions on the buttocks and legs. The lesions began as white urticaræ 0.5 to 1 cm. diameter, adjacent lesions coalescing. The central part soon turned red and this change spread centrifugally until the white urticarial papule had been transformed into a dusky red papule, whose colour did not fade on pressure. This change took place within the space of an hour. Within 24 hours the red papules had become darker and flatter, and gradually faded to red-brown macules which after two weeks faded completely. The infant received a course of sulphamezathine and penicillin and made a rapid recovery, the swelling of the legs clearing within three days and the otitis resolving within a week. The urine was normal throughout.

Biopsy of skin lesions, both urticarial and maculo-papular, showed a similar histology which conformed to that already described for the skin lesions in the Schönlein-Henoch syndrome as seen in older children and adults, consisting of a perivascular inflammatory exudate of polymorphs with eosinophils and histiocytes, there were scanty red cells.

The exanthem in this case thus conformed both clinically and histologically to the picture of the Schönlein-Henoch syndrome in older patients. The florid lesions seen on the cheeks are not commonly seen in the older patient, but that they may so occur was shown by Case 9, a 12-year-old boy who had well-marked purpuric lesions on the cheeks. Similar cases have been occasionally reported in the literature under a variety of names, cockade purpura (Seidlmayer, 1939, Opitz, 1943), allergic purpura (Njá, 1945), and erythema multiforme haemorrhagicum (Heinild, 1943). From the descriptions and illustrations it is clear that all these refer to the same condition, a composite picture of which is as follows. An infant of from six months to three years who has recently recovered from an upper respiratory tract infection develops a florid rash on the face, ears, and extensor surfaces of the extremities. The rash is at first urticarial,

rapidly becoming maculo-papular or purpuric. Swellings, of the legs and face especially, occur. Bleeding occasionally takes place from the gut or kidneys. A biopsy in Heimild's (1943) case is of special interest. In addition to the acute perivascular inflammation as seen in our case, some small skin vessels showed necrotizing inflammatory changes. From the study of our patient and of the cases of the other authors quoted it may be concluded that after an upper respiratory tract infection in infants and children in the six months to three years age-group there may develop an acute exanthem which clinically and histologically conforms to that seen in the Schönlein-Henoch syndrome. Swellings of the extremities or face occur at the same time. This condition exhibits a pattern so like that of the Schönlein-Henoch syndrome that it should be regarded as the form which this syndrome takes in infancy. Accordingly it may be referred to as the infantile form of the Schönlein-Henoch syndrome.

Purpura fulminans and post-scarlatinal gangrene. Although lacking personal experience of these two rare conditions, a short account of them has been included since the available evidence suggests that they are variants of the Schönlein-Henoch syndrome, and their study may shed some light on the nature of the latter. Henoch (1887, 1899) first described purpura fulminans as follows:

'haemorrhages from mucosal injuries are completely lacking, but huge ecchymoses appear with enormous rapidity which, within a few hours colour the whole extremities blue and red-black with an indurated sanguineous infiltration of the cutis. Although in two cases there occurred sero-sanguineous blisters in the skin, gangrene never occurred. The course is enormously swift, scarcely 24 hours elapsing between the formation of the first haemorrhages and death, the longest duration was four days. Hence complications are lacking, and autopsy produced a completely negative result (apart from a generalized anaemia), in particular there was no trace of an embolic or thrombotic process. One of my cases developed two days after the crisis of a pneumonia, the other one and a half weeks after a mild scarlet fever. In two other cases there was no such aetiological relation.'

In spite of the definite relation to infection in some cases I should like for the moment to separate this form from the other forms of purpura, not only because of its fulminating and fatal course, but also because of the absence of internal and mucosal haemorrhages.

Since Henoch's time further cases largely conforming to this description have been reported, some with recovery, some cases have also developed gangrene. Elliott in 1909 was able to collect records of 55 cases from the literature and added one of his own. Although no doubt some of these cases were meningococcal or other septicaemias, yet in none of the 12 cases of Elliott's series where autopsies were performed was suprarenal haemorrhage noted, which makes it unlikely that these fatal cases were due to meningococcal infection. Further cases have been published since the signs of meningococcal septicaemia became well known, these are listed by Glanzmann (1937). It may be concluded that the condition of purpura fulminans exists apart from septicaemic conditions. Of the 56 cases collected by Elliott twice as many male as female patients were affected (32 male to 15 female, and sex not stated in nine). The majority of cases (47 out of 56) were in children below the age of 10 years, including some

young infants Large symmetrical areas of purpura involved generally the extremities, the buttocks, the lower back, and the face, bleeding from the gut and kidneys sometimes occurred, in Elliott's own case the renal histology showed an acute nephritis In all these ways purpura fulminans resembles the Schönlein-Henoch syndrome. Particular interest attaches, therefore, to the histology of the skin lesion described in Elliott's case of purpura fulminans, the most marked changes were found in the corium, which showed necrosis with a polymorphonuclear cellular infiltration along with red cells, the polymorphonuclear infiltration also involved adjacent layers of the epidermis and subcutis, and vesicles filled with polymorphs were present These changes, being those of an intense acute inflammatory reaction, are similar to, though more intense than, the skin lesions described in the Schönlein-Henoch exanthem In the majority of published cases purpura fulminans has followed an infection, and in 16 out of 56 cases (Elliott, 1909) this infection was scarlet fever, the purpura generally developing about three weeks after, at the time, that is, when post-scarlatinal nephritis occurs In Elliott's own case, for instance, on the 17th day after mild scarlet fever a second attack of tonsillitis occurred, the urine then containing albumen and granular casts, two days after this the purpura appeared.

This relation of purpura fulminans to scarlet fever draws attention to another rare complication of the latter, post-scarlatinal gangrene, of which 21 cases have been reported to date, the majority in children (Webb, Dubs, and Conrad, 1947) Typically, two or three weeks after a mild attack of scarlet fever and often after a second attack of pharyngitis or cervical adenitis, there suddenly appears a symmetrical gangrene of the extremities and buttocks, with sometimes an accompanying purpuric rash In eight of 11 cases collected by Dick, Miller, and Edmondson (1934) there was also a nephritis and in one case gastro-intestinal haemorrhage Though amputation has frequently been necessary, recovery has been the rule in the more recent cases Material from amputations and from autopsy has been examined in a number of cases (Dick, Miller, and Edmondson, 1934) Thrombi are sometimes present in the arteries and veins of the affected extremities, possibly secondary to the gangrene rather than its cause, since in other cases the larger vessels are normal and unobstructed A clue to the pathogenesis of the condition is furnished by the histological findings in Hoyne and Smollar's (1941) case where sections of muscles just above the level of the gangrene showed an acute myositis and a panarteritis affecting the arterioles Clinically there is no clear distinction between post-scarlatinal gangrene and purpura fulminans, several cases of the latter (e.g. Elliott's Cases 1, 9, and 10) having exhibited both massive purpuric and gangrenous lesions In post-scarlatinal gangrene also there is a preponderance of male patients, eight male to three female in Hoyne and Smollar's (1941) collection of cases The Schönlein-Henoch exanthem (which, as in Case 2 of the present series, may proceed to local gangrene of the skin), purpura fulminans, and post-scarlatinal gangrene may thus be the result of the same pathological process, an acute aseptic inflammation acting with different degrees of severity upon the skin and, in the gangrenous cases, upon the deeper tissues If the contention is accepted that the Schönlein-

Henoch syndrome is closely related to purpura fulminans and to post-scarlatinal gangrene, both of which frequently occur about three weeks after scarlet fever, these facts provide further evidence relating the Schönlein-Henoch syndrome to a preceding haemolytic streptococcal infection

Treatment

No treatment has been proved to have any effect upon the course of the illness. Rest in bed in one patient (Case 11) temporarily controlled the exanthem when this was chiefly on the ankles, but in others the exanthem has continued to recur even when the patient was kept in bed. Similarly haematuria has not been modified by rest, and it has often been a problem how long to keep these patients in bed. Penicillin has been tried in three patients (Cases 5, 6, and 11), sulphonamides in one (Case 5), and protein shock in one (Case 11), in all without effect. In Case 11 there was a chronic purulent tonsillitis from which a heavy growth of haemolytic streptococci was repeatedly obtained, after tonsillectomy, although the throat swab became negative for haemolytic streptococci, the exanthem continued to appear. Salicylates have been given for the arthralgias without the relief characteristic of rheumatic arthritis, and observed in the two patients (Cases 10 and 11) who developed rheumatic fever. In the literature there are occasional reports illustrating the existence of avitaminoses in cases of the syndrome, sometimes with claims that relief followed exhibition of the appropriate vitamin. Vitamins C and P (citrin) have already been mentioned in the section on capillary resistance. A low prothrombin level in the blood has been reported by Hoet and van Vyve (1940) and Jelke (1946), in an infantile case by Njå (1945), and in a case of post-scarlatinal gangrene by Webb, Dubs, and Conrad (1947). Schaad (1941) also has claimed success in treating a case with vitamin K. The prothrombin level was normal in Case 13 of the present series, in Jelke's (1946) case, in spite of the low prothrombin level, the exhibition of vitamin K did not prevent relapses. A knowledge of the natural history of the condition with its spontaneous recoveries and later relapses should breed a sceptical attitude towards therapeutic claims based on few observations.

Discussion

Definition of the Schönlein-Henoch syndrome It has been shown that there exists a type of skin rash which is recognizable both clinically and histologically. This rash, which for want of a better name may be termed the Schönlein-Henoch exanthem, is found associated at different times with certain gastro-intestinal symptoms, joint symptoms, swellings of the face and extremities, and nephritis. Although the clinical picture resulting from different combinations of these symptoms varies widely, common to all of them is the well-defined exanthem, and this fact makes it possible to define the whole group as a clear entity. Reasons have also been advanced for bringing purpura fulminans and post-scarlatinal gangrene within the group, since the pathology of the skin lesions in both these conditions is suggestively similar to that of the Schönlein-Henoch exanthem.

Pathogenesis That the various manifestations of the Schönlein-Henoch syndrome are all the result of a vascular lesion seems probable. In the skin this has been already shown. The more severe gastro-intestinal symptoms have been shown to be the result of serous or sanguineous extravasations into the gut wall, which points to a vascular origin, and this has usually received support in the few cases where the histology of the gut lesions has been recorded. The frequent existence of a nephritis implies involvement of the capillaries of the glomeruli. The origin of the joint symptoms must remain a matter of surmise since we lack pathological studies of the lesion. Clinically, however, the joint symptoms resemble those of serum disease, pain and tenderness are the usual findings, and swelling, where present, appears to be more often due to periarticular oedema than to effusion into the joint. This clinical resemblance suggests that the pathogenesis of the joint symptoms in the Schönlein-Henoch syndrome may be similar to that of serum disease, that is, that both result from a vascular reaction, which is probably an acute aseptic inflammatory one, since Boots and Swift (1923) showed that the joint exudate in serum disease was polymorphonuclear in acute cases. If the various symptoms of the Schönlein-Henoch syndrome are the result of a vascular disorder, the nature of this must next be considered. In the skin the lesion has been proved to be an acute inflammation around the smaller blood-vessels, often with a tissue eosinophilia. The necrotizing arteriolitis which has been found on occasions in the skin, gut, and brain presumably represents a severe degree of the same process. Reasons have been given for attributing purpura fulminans and post-scarlatinal gangrene to an analogous vascular condition. Thus the protean manifestations of the Schönlein-Henoch syndrome can be ascribed to a common lesion, an acute aseptic inflammatory vascular reaction proceeding in severe cases to a necrotizing arteriolitis. An acute aseptic perivascular inflammatory reaction with eosinophilia suggests an anaphylactic reaction. The experiments of Abell and Schenck (1938) are relevant here. They sensitized a rabbit to horse-serum and observed the vessels of its ear with a microscope. After the introduction of antigen (horse-serum) there was arteriolar spasm, emigration of leucocytes, and (if antigen was repeatedly introduced) extravasation of erythrocytes and endothelial destruction. The cutaneous lesions of the Schönlein-Henoch syndrome might well be accounted for by such a process. There is thus some reason for regarding the Schönlein-Henoch syndrome as the result of a process akin to anaphylactic (Arthus type) hypersensitivity, and so for postulating an antigen-antibody interaction such as takes place in anaphylaxis (Mackenzie and Leake, 1921). Experimental evidence bearing on this theory is scanty. Schittenhelm (quoted by Glanzmann, 1916) in some old experiments with anaphylactic shock in dogs, produced a haemorrhagic condition of the gut which he termed anaphylactic enteritis. More recently Li (1941) has reported that relapses can sometimes be induced in children who have recovered from the Schönlein-Henoch syndrome by the intravenous administration of serum from other cases of 'purpura', and suggested that the mechanism of reversed anaphylaxis was operative.

Aetiology In over half of the patients there was evidence that an infection shortly preceded attacks of the syndrome, and reasons for considering the haemolytic streptococcus as chiefly responsible for these infections have been given. The time relationship between an infection and the subsequent attack of Schönlein-Henoch syndrome is of interest. If a first attack of the syndrome were preceded by a sore throat, there was an interval of from one and a half to four weeks between the two. If, however, a subsequent sore throat precipitated a relapse this interval was shortened, being seven days or less in the four cases studied, and less than 24 hours in two of these. This shortening of the incubation period is reminiscent of the 'anamnesic reaction' which occurs in anaphylactic responses subsequent to the first reaction (Mackenzie and Leake, 1921) and provides a further analogy between the Schönlein-Henoch syndrome and anaphylaxis. It is noteworthy that a similar phenomenon has been observed in rheumatic fever (Schlesinger, 1930). Although no case of food hypersensitivity has been personally encountered, reasons have been given for believing that this may occasionally cause the syndrome. The conclusion is thus reached that the Schönlein-Henoch syndrome is due to a hypersensitivity reaction, where the antigen may be either bacterial or non-bacterial in origin.

Relation of the Schönlein-Henoch syndrome to acute nephritis, rheumatic fever, and polyarteritis nodosa It has been shown that the Schönlein-Henoch syndrome frequently coexists with nephritis, and occasionally with rheumatic fever. The necrotizing arteriolar lesions found provide a suggestive pathological link with polyarteritis nodosa, which with its varying manifestations has also an impressive clinical resemblance to the Schönlein-Henoch syndrome. In both conditions there may be crops of urticarial and purpuric skin lesions, oedema, episodes of visceral symptoms, and haematuria and nephritis (Spiegel, 1936), in both, male patients are affected two to three times as often as female patients (Miller and Daley, 1946), indeed the Schönlein-Henoch syndrome and polyarteritis nodosa may well be regarded as essentially the same disease, the capillaries being involved in the one and the arteries in the other, arteriolar lesions being common to both. The three conditions of acute nephritis, rheumatic fever, and polyarteritis nodosa also show a tendency to coexist. In polyarteritis nodosa rheumatic heart lesions were found *post mortem* in six of 13 of Friedberg and Gross's (1934) series and in 5 of 17 of Spiegel's (1936) series, in about one-third of autopsy cases glomerulonephritis is present (Miller and Daley, 1946). The association between nephritis and rheumatism is, however, less striking, for although Loeb (1944) mentioned that '25% of patients dying of acute nephritis at the Presbyterian Hospital were shown at autopsy to have associated active rheumatic disease', this important finding has not yet been reported elsewhere, while a consideration of the results of others (Coburn, 1931, 1944, McCann, 1935, Salvesen, 1938, Nathhorst, 1940) leads to the conclusion that clinically rheumatic fever coexists with only two or three per cent of cases of nephritis, and that a true nephritis complicates rheumatism in about the same small proportion of cases. These four conditions, Schönlein-Henoch syndrome, acute nephritis, rheumatic fever, and polyarteritis nodosa,

are also linked aetiologically by their relationship to the haemolytic streptococcus. This relationship was present in at least half of the cases of the Schönlein-Henoch syndrome, in acute nephritis (Loeb, 1944) and rheumatic fever (Swift, 1944) it is present in the great majority of cases. In polyarteritis nodosa a variety of infections has been reported, but where a specific organism has been found this is more often the haemolytic streptococcus than otherwise (Miller and Daley, 1946). In Spiegel's (1936) series there was an upper respiratory tract infection (acute tonsillitis or sinusitis) immediately preceding the onset of the polyarteritis illness in seven of 17 cases, and in two further cases the patient

TABLE III

Summary of evidence indicating type of antigen (bacterial or non-bacterial) in certain diseases possibly due to hypersensitivity

	<i>Rheumatic fever</i>	<i>Acute nephritis</i>	<i>Schönlein-Henoch syndrome</i>	<i>Polyarteritis nodosa</i>
Occurrence of associated streptococcal infection	In over 90% of cases	In over 80% of cases	In over 50% of cases	Frequently
Occurrence in the course of conditions due to non bacterial hypersensitivity	No	Occasionally	Occasionally	Frequently
Production by experimental anaphylaxis	? Yes	Yes	Doubtful	Yes

had had scarlet fever two months previously. While it thus appears that all four conditions may be provoked as a result of sensitization to streptococcal products, at other times sensitization to non-bacterial substances may be causative, as has already been shown to be the case in the Schönlein-Henoch syndrome. In polyarteritis nodosa hypersensitivity to horse-serum and other non-bacterial substances has appeared to initiate the disease in many instances (Miller and Daley, 1946). Acute nephritis has occasionally been reported as occurring in serum disease or other anaphylactic states (Ehrström, 1941). Experimentally the recent work of Rich and Gregory (1943 *a, b*) is pertinent. They induced serum reactions in rabbits, some of which developed widespread polyarteritis nodosa, some developed also glomerulonephritis, while yet others showed heart lesions having 'the basic characteristics of rheumatic carditis'. If these results can be confirmed they provide striking support for the unitary concept of these three diseases. On the hypothesis that all four conditions are the result of hypersensitivity, some cases involving bacterial antigens and others non-bacterial antigens, the foregoing facts are summarized in Table III.

If a mechanism akin to anaphylaxis be responsible for this group of conditions it would be expected that the site of the lesion in all would conform to the findings in anaphylaxis, where blood-vessels and smooth muscle are the only tissues upon which the antigen-antibody reaction is known to operate (Rich and Follis, 1940, Rich, 1944). In the Schönlein-Henoch syndrome, as has already been shown, a vascular lesion can account for all the varied manifestations. In acute nephritis

the vascular lesion is evident in the glomerular capillaries, and a generalized capillaritis has also been held to account for the oedema of acute nephritis. Polyarteritis nodosa is a disease of medium-sized arteries and arterioles with characteristic pathological changes. Of the four conditions it is only in rheumatic fever that a primary vascular disease is not clearly evident, there is nevertheless certain evidence favouring such a pathogenesis in this condition also. A generalized arteriolitis in rheumatic fever occurs in a proportion of cases (Von Glahn and Pappenheimer, 1926) and is with difficulty distinguishable from polyarteritis nodosa, as was first noted by Aschoff himself in 1904. The Aschoff bodies, foci of collagen degeneration, generally lie adjacent to a blood-vessel which may itself be the seat of rheumatic arteritis, as is figured in Swift's (1944) article. In erythema annulare also the inflammatory cells grouped chiefly around blood-vessels suggest that this rheumatic manifestation has a vascular origin. Thus it is possible that the collagen damage which constitutes the typical histological lesion in rheumatism is itself secondary to a pathological process occurring in the adjacent vessel.

Conclusions

Evidence has been assembled to show that the Schönlein-Henoch syndrome, acute nephritis, rheumatic fever, and polyarteritis nodosa together form a family of diseases, linked by the tendency for one member to coexist with another, and by other characteristics common to the group. The pathogenesis common to the members of this group is probably an antigen-antibody reaction, akin to that occurring in anaphylaxis, and taking place especially in the endothelium of certain blood-vessels. The commonest antigen is a derivative of the haemolytic streptococcus, although proteins derived from other organisms or from non-bacterial sources may also act. The blood-vessels especially involved in this way are in the Schönlein-Henoch syndrome the small vessels of the skin, gut, synovia, or glomeruli, in nephritis the glomerular capillaries, and in polyarteritis nodosa the medium-sized arteries and arterioles. In rheumatic fever the site of the reaction is less clear, but it is possible that here too the predominantly connective tissue damage is secondary to vascular lesions such as are sometimes demonstrable. Although there is much in the clinical and pathological pattern of this family of conditions to link it with anaphylactic phenomena, the failure up to the present to demonstrate the antigen concerned (only surmised to exist by analogy with the findings in anaphylaxis) must constitute a bar to our understanding of that group of diseases which is believed to result from bacterial hypersensitivity. In the Schönlein-Henoch syndrome there exists a member of this group which deserves attention, since its skin manifestations provide a lesion which is readily accessible for study by both clinician and pathologist.

Summary

1 A study of 12 cases of the Schönlein-Henoch syndrome shows this to be characterized by an exanthem which is recognizable both clinically and histologically. The skin lesions are due to perivascular inflammation, haemorrhage is

a variable feature and probably consequent on the inflammatory process. A similar pathogenesis probably accounts for the gastro-intestinal, articular, and renal symptoms. In severe cases the vascular lesion may amount to a necrotizing arteriolitis.

2 In infancy the syndrome occurs with some special features.

3 Purpura fulminans and post-scarlatinal gangrene are probably variants of the Schönlein-Henoch syndrome.

4 Haemolytic streptococcal respiratory tract infections were associated with the syndrome in more than half the patients. Food hypersensitivity may occasionally provoke the syndrome. A hypersensitivity mechanism akin to that of anaphylaxis probably operates, and the sensitizing agent may be either bacterial or non-bacterial.

5 Nephritis is commonly associated with the syndrome and rheumatic fever occasionally so.

6 Clinically, pathologically, and aetologically, the Schönlein-Henoch syndrome is linked with acute nephritis, rheumatic fever, and polyarteritis nodosa. A pathogenesis common to this group of conditions is suggested.

Professor J. C. Spence suggested the subject of this study. I am indebted to the late Professor Bernard Shaw and to Drs J. G. Thompson and H. G. N. Richards for advice on pathological matters. The staffs of the Royal Victoria Infirmary and the Newcastle General Hospital have given me free access to patients under their care. Dr Brenda Morrison's notes on some of the patients were of great assistance. To all these colleagues my thanks are due.

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FIG. 2 (Case 7) Macular phase of exanthem on backs of elbows. The lesions are characteristically slightly more numerous on the right arm.

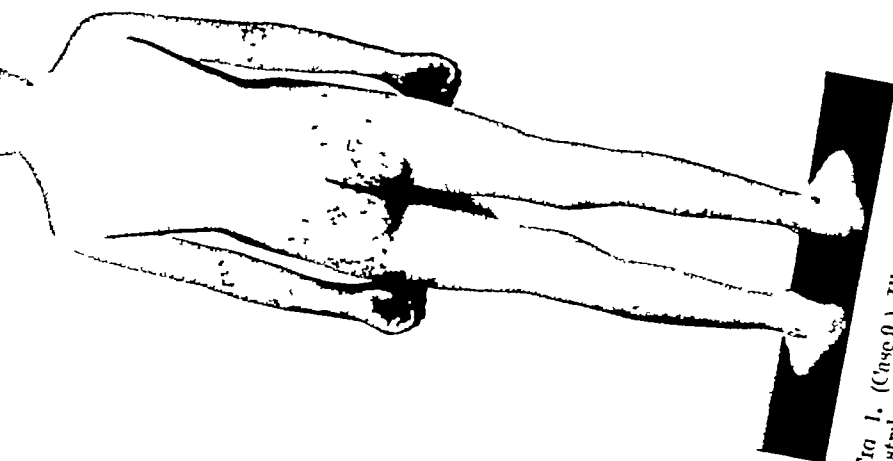
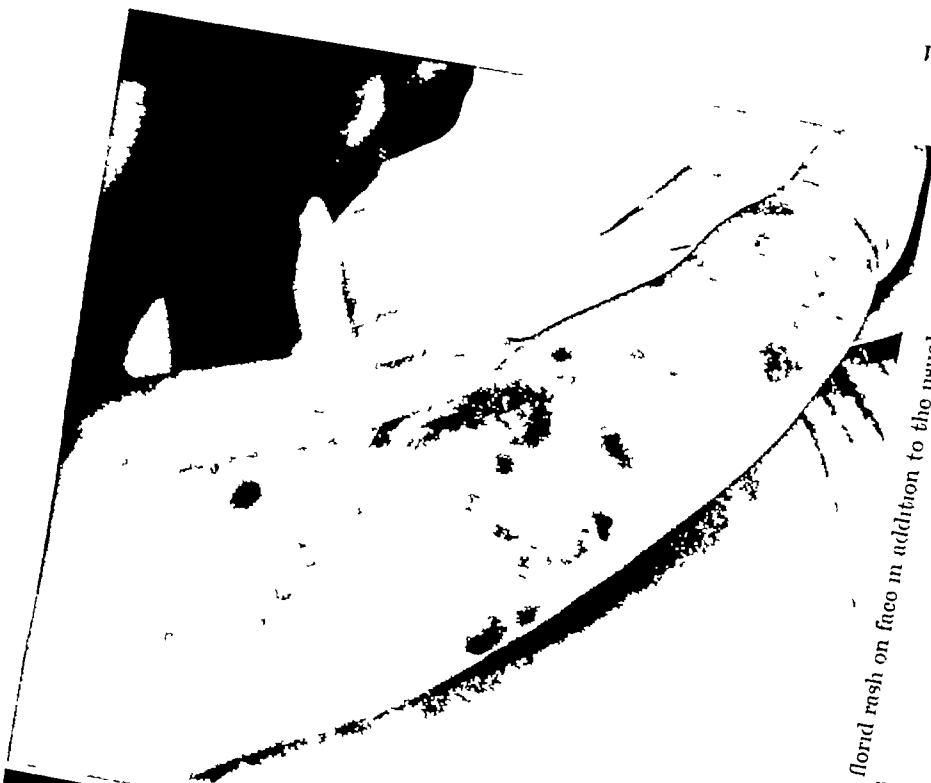


FIG. 1. (Case 9) Illustrating the usual distribution of the Schönlein-Henoch exanthem on backs of elbows, buttocks, and ankles.

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FIGS 5, 6 (Case 13) Schönlein-Henoch exanthem in infancy. Note florid rash on face in addition to the usual involvement of extremities



Fig 3 (Case 2) Gross purpuric and necrotic lesions on buttocks the curved marks correspond to the edge of the bed pan



Fig 4 (Case 6) Confluent lesions on front of feet and ankles

A CASE OF CHRONIC PORPHYRIA ASSOCIATED WITH RECURRENT JAUNDICE¹

By CHARLES H. GRAY, C. RIMINGTON, AND SYDNEY THOMSON

With Plate 14

Introduction

THIS paper describes a case of porphyria, the clinical and chemical features of which are difficult to classify under any of the known forms of the condition. Our investigations lead us to believe that a hitherto undescribed porphyrin was excreted in the urine during the active phases of the disease. Although attempts to isolate and characterize this pigment have so far been unsuccessful, we feel justified in presenting our findings on account of the unusual interest attaching to the case.

The most acceptable classification of the porphyrias is that due to Waldenström (1937) who recognized the following groups:

1 *Porphyria congenita*. A familial disease, probably recessive in character, present at birth, and characterized by sensitivity to light, pigmented bones and teeth, and greatly increased coproporphyrin and uroporphyrin excretion, mainly of series I.

2 *Porphyria cutanea tarda*, in which the porphyrinuria and sensitivity to light develop later in life and a sclerodermic tendency is noticeable. The occurrence of colic and the occasional excretion in the urine of large quantities of uroporphyrin III suggest a relationship with the form next to be described. Severe nervous symptoms are not present.

3 *Porphyria acuta*. A familial disease accompanied by the excretion of coproporphyrin and uroporphyrin, mainly of series III. The following clinical forms have been recognized:

(a) Latent porphyria in which there is increased uroporphyrin excretion without any clinical manifestations of porphyria. Such cases as have been encountered have always been relatives of patients with overt forms of the disease (see (b), (c), (d) and (e)).

(b) The pure abdominal form with abdominal symptoms but no paralyses.

(c) The pure nervous form with paralyses but no abdominal symptoms.

(d) Classical acute porphyria with colics and paralyses.

(e) The comatose form in which the coma of the terminal stage predominates.

As will be seen from the description below, our case shows most similarity to porphyria cutanea tarda in that colic and sensitivity to light developed in early manhood, while nervous symptoms were never present. Increased urinary

¹ Received September 25, 1947.

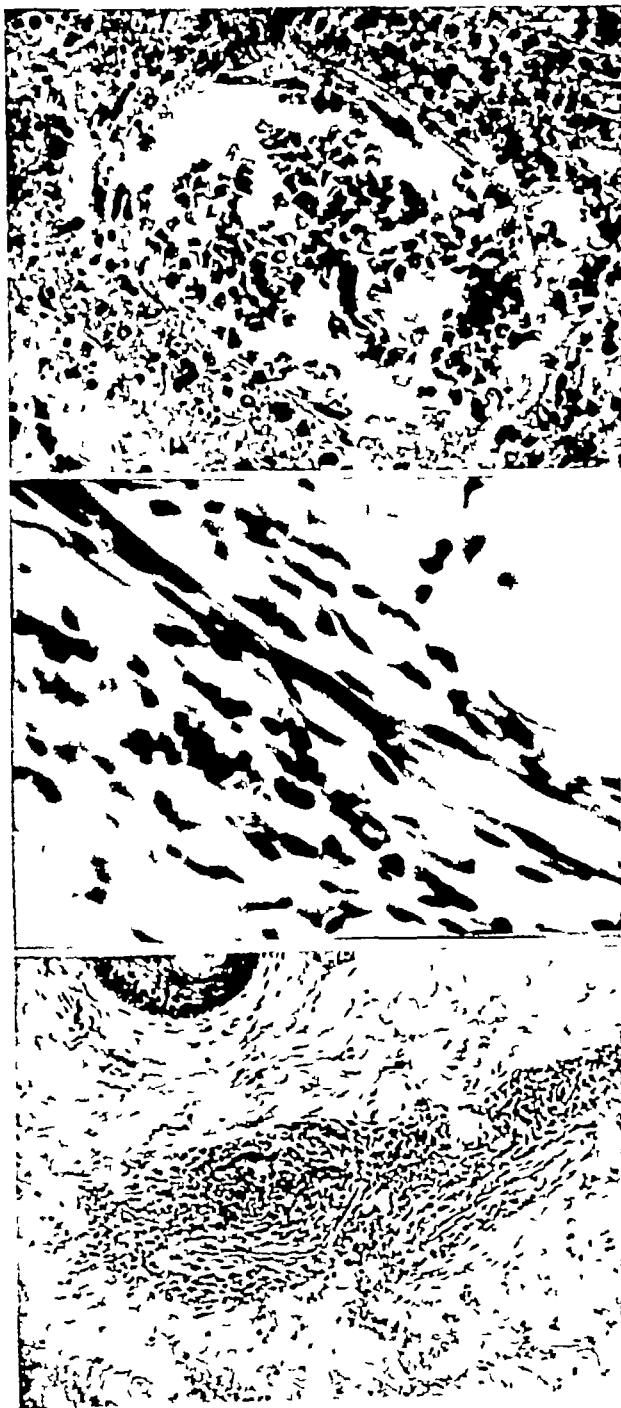


Fig 7 (Case 11) Schönlein-Henoch syndrome. Skin biopsy ($\times 157$), showing small vessels in dermis with perivascular inflammatory exudate. The cells are polymorphs with numerous eosinophils and histiocytes, there are no red cells

Fig 8 (Case 5) Skin biopsy ($\times 510$), slight exudate around small vessel in dermis, the cells are polymorphs with some eosinophils, there are no red cells

Fig 9 (Case 2) Arteriole in cerebral meninges ($\times 370$), showing necrotizing arteriolitis. The vessel wall is infiltrated with cells, including eosinophils

2 1 42 he was obviously jaundiced again and on 3 1 42 there was a return of his abdominal pain. The urine remained dark and the faeces pale until about the middle of January. He was discharged from hospital on 1 2 42. Between this time and 22 5 42 he had three minor attacks of abdominal pain each lasting for two or three days. During the first of these attacks he noticed that his eyes were yellow. He had no further skin lesions until 5 5 42 when a single vesicle 1 mm in diameter appeared on his hand. On 22 5 42 he was admitted to King's College Hospital again with another abdominal episode identical with that experienced in August, 1941. Again, there was slight jaundice. At this time he was beginning to get, on going into the sunshine, a crop of vesicles on the exposed surfaces of the skin and in addition experienced considerable puffiness and swelling of the forehead and face, a symptom which he had noted on previous occasions prior to his admission to King's College Hospital. On examination there were numerous ulcerated areas scattered over the face and hands. These had begun as bullae of varying sizes which had then ruptured, leaving haemorrhagic scabs. By 16 6 42 the attack of abdominal pain and jaundice had cleared up and confinement in bed had been associated with considerable improvement in the skin conditions, which had been treated with a protective ointment of quinine sulphate 5 per cent in soft paraffin. From this time until May 1943 the skin symptoms were minimal, but he experienced two moderately severe abdominal attacks. On most occasions the patient stressed the fact that each abdominal attack was ushered in with a feeling of urgency of micturition, a feature which has been mentioned in the report of a somewhat similar case by Taylor, Solomon, Weiland, and Figge (1946). In May 1943 he was admitted to Horton Hospital with an extensive crop of vesicles and a sharp attack of abdominal colic. Jaundice was again present. This abdominal episode was of short duration. At this time it was very striking that pure photosensitivity had become much more prominent, whereas previously photosensitivity had been combined with sensitivity to trauma. He made rapid improvement and was discharged almost symptomless on 15 5 43. He was not seen again until 7 5 46 when he reported at King's College Hospital that he had been well for three years except for a few mild attacks of abdominal pain. He had not noticed any yellowness and there had been no skin eruptions for three years. In February 1947 he had his most recent attack of abdominal pain and a month later one vesicle had developed on his face. There have been no further symptoms up to June 1947. Constipation has never been a feature. Treatment has been varied and probably has contributed little to any improvement in his condition. At various times the abdominal episodes were treated with calcium gluconate, with dehydrocholic acid, with bromide and chloral, and on one occasion with morphine. His attack in May 1943 was treated with intensive alkali therapy, the alkali reserve being raised to 76 volumes per cent. This acute attack cleared up dramatically. During the last four years he has received no special treatment, but his skin sensitivity has cleared up and the abdominal symptoms have never been severe.

We thus see that the history falls naturally into four stages

- 1 Normal health up till the age of 20 years
- 2 A period lasting two years in which summer-time photosensitivity associated with direct local trauma predominated, but during which there were no abdominal symptoms
- 3 A period of two years during which sharp attacks of abdominal pain occurred at relatively frequent intervals. The earliest and more severe attacks

porphyrin excretion was observed, but no uroporphyrin III could be isolated as has been possible from some cases of porphyria cutanea tarda

Case History

The patient was admitted to King's College Hospital in March 1941, under the care of one of us (S T). He was a young man of 22 years when first seen and had been perfectly well until October 1939. As a child he had had the usual childish complaints, but gave no history of skin trouble or jaundice or other diseases involving the liver. No abnormal colour of the urine had ever been noticed. In 1937 he joined the regular army and led a vigorous outdoor life, for several years playing a prominent part in army boxing. He gave no history of easy injury of the skin and never experienced any abnormality in the healing of abrasions due to boxing. His troubles began in 1939 when his duties as a dispatch rider were inconvenienced by skin lesions of his face and hands. The obscure nature of these skin lesions is well shown by the various diagnoses suggested by the medical officers to whom his malady led him for advice. At various times the following had been seriously considered: bullous impetigo, blood-poisoning of the face, cheilopompholyx, pyoderma of the hands and legs, generalized pruritus with secondary infection, erysipelas of the face, and severe Quincke's oedema of face. Examination revealed a young man of excellent general physique. The skin of his face and forearms presented a large number of bullous areas of varying size, the largest being 5 cm. in diameter. Some of these bullae were at the stage of healing, yielding fairly deep scabs which, however, healed well, leaving none of the typical scarring of *hydroa aestivale*. The condition was considered to be either a curiously localized dermatitis herpetiformis or *hydroa aestivale*, and his urine was therefore examined for porphyrin. This was first found in considerable excess on 5.4.41. There was no history at this time of abdominal colic or of periods of constipation. His skin showed only a slight reaction to the light of a mercury vapour lamp in doses equal to 16 times the normal erythema-producing dose.

Throughout the summer he developed further outbreaks of vesicles and on 1.8.41 was confined to bed with his first attack of abdominal colic. The pain was epigastric in distribution and tended to be continuous, but was relieved by hot fluids by mouth. There was anorexia and nausea for a short time but no vomiting. His temperature, pulse-rate, and rate of respiration were all slightly raised. The liver, spleen, and kidneys could not be felt, but there was pain and guarding in the epigastrium. No abnormality in the respiratory, cardiovascular, or central nervous systems could be found. The sclerotics were noticed to be slightly jaundiced. There was no constipation. The stools were clay-coloured, and bilirubin and urobilin were present in the urine. The abdominal pain cleared up within a week, but on 12.8.41 the sclerotics were still slightly yellow. He was allowed out in the sunshine on 19.8.41 and on the following day a few new vesicles appeared for the first time since his confinement to bed with the onset of abdominal pain. On 24.9.41 it was noted that light tappings with a stick produced first-degree erythema within half an hour, and that bullae subsequently developed within six hours in some of these areas of erythema. This suggested that trauma as well as exposure to light might be a causal factor for the skin lesion. On 22.10.41 he was seen by Professor S. Nevin who could find no abnormality of the central nervous system. No more vesicles developed and he remained relatively well until 28.12.41 when he complained of generalized irritation of the skin unrelieved by scratching. Three days later he noticed that his urine was dark in colour and on 1.1.42 he vomited. On

'The section shows a rounded mass of relatively acellular fibrous tissue containing a great deal of sweat gland tissue. It is covered by stratified epithelium with much piling up of keratin on the surface.'

Porphyrin Determinations

Repeated qualitative investigations of urine and stools during 1941 and 1942 revealed that at times of increased light sensitivity and abdominal pain the urinary porphyrin excretion was always above normal and that the faecal porphyrin was only just qualitatively detectable by Snapper's technique. On

TABLE I
Urinary Coproporphyrin Excretion

Date	Volume c.c.	Mg per diem
6-7/1/42	640	1.81
7-8/1/42	930	2.75
8-9/1/42	1385	3.20
9-10/1/42	1385	3.95
10-11/1/42	1220	2.60
11-12/1/42	1420	3.97
12-13/1/42	1245	3.34
13-14/1/42	960	2.18
14-15/1/42	960	1.60
15-16/1/42	845	1.88
16-17/1/42	1015	2.36
17-18/1/42	1130	1.68
18-19/1/42	620	1.12
22-23/1/42	1810	0.79
23-24/1/42	1700	0.97
24-25/1/42	1810	0.88
25-26/1/42	—	(0.74 per litre)
26-27/1/42	680	0.43

the other hand, during times of remission the urinary porphyrin appeared normal, but the faecal porphyrin excretion was so greatly increased that the whole faecal material fluoresced bright red in ultra-violet light. Such qualitative observations were confirmed by quantitative determinations. Twenty-four-hour specimens of urine passed during periods of remission of the disease were analysed and afforded figures of 41 to 55 μgm of ether-soluble porphyrin per 24 hours, a value within normal limits. Ether-insoluble porphyrins could not be detected in such specimens. Table I presents the results of urinary coproporphyrin determinations performed during one of the patient's major abdominal attacks. At such times there was always present a great excess of coproporphyrin together with approximately an equal amount of ether-insoluble porphyrin. On only two occasions was it possible to determine quantitatively the total daily urinary and faecal pigment excretion, once during the attack and once during remission. On both occasions stools were collected over a period of eight days. The results, together with those of determinations of urinary and faecal stercobilin and stercobilinogen, are presented in Table II. An analysis of a sample of bile, obtained by duodenal intubation on 10.4.42, showed a content of 1.92 mg of ether-soluble porphyrin per 100 c.c. More recently

were associated with attacks of jaundice, but did not appear to be related to the season. During this phase photosensitivity associated with direct local trauma was present in summer-time and was particularly marked about the time of the abdominal attacks.

4 A period of four years, lasting up to the time of writing, during which the attacks of abdominal pain became less severe and less frequent. At the same time, photosensitivity had diminished so much that during the whole of this phase only one vesicle appeared, despite considerable exposure to sunlight during the last two years. There was no evidence that any of the patient's relatives had suffered from a similar illness.

It is interesting that during the early part of phase 3 both exposure to light and to trauma appeared to be necessary for the development of vesicles. Vesicles tended to appear only on those exposed areas which were subjected to mild mechanical trauma such as by friction of a degree insufficient to produce damage in a normal person. The vesicles appearing during the second phase cannot have been associated with the combined sensitivity to light and trauma since there is evidence that the abrasions due to boxing healed with normal rapidity. During the latter half of phase 3 trauma appeared to become less significant and photosensitivity again became the dominant factor in the causation of the skin lesion. Of even greater interest was the association of jaundice with each of the major abdominal episodes. Repeated haematological investigations failed to reveal any evidence of excess haemolysis or other haematological abnormality, nor has there been any evidence of gallstones or other disease of the biliary tract. The clinical history, the pale stools, and the appearance of urobilin as well as bilirubin in the urine leave little doubt that the jaundice was hepatogenous in origin. The results of tests of hepatic function agree with this view. The laevulose tolerance and galactose tolerance were not impaired, but the oral hippuric acid test gave a result of 60 per cent. of normal compared with 150 per cent. of normal when performed in the absence of jaundice. The jaundice was never intense, the highest level of serum-bilirubin being 4.0 mg per 100 c.c. An epidemic of acute hepatitis prevailed at the time when our patient was experiencing attacks of jaundice. There was no pigmentation of the teeth as occurs in congenital porphyria, nor did they show red fluorescence when examined in ultra-violet light. At times when the patient was sensitive to light a red fluorescence could be seen when his blood-serum was illuminated by ultra-violet light. During the abdominal attacks the fluorescence of the serum became much more intense and, as far as could be judged by mere inspection, must then have corresponded to a serum-porphyrin content of about a milligram per 100 c.c. The greater part of this serum-porphyrin was not extractable with ether and acetic acid, and thus behaved differently from coproporphyrin and erythrocyte protoporphyrin, which are readily extractable by these reagents. The fluid obtained by puncture of the vesicles also fluoresced red in ultra-violet light and probably contained porphyrin in a concentration of about 100 μ gm per 100 c.c. A biopsy of one of the vesicles from the hand was performed in September 1941. Dr E. ff. Creed kindly reported as follows:

of small needles, melting-point 143° , remelting-point 162° C, corresponding to coproporphyrin III tetramethyl ester. The trace of ether-insoluble ester was insufficient for identification, but in a later experiment, using six litres of urine and during an attack, coproporphyrin I was identified (together with larger amounts of coproporphyrin III methyl ester) after several recrystallizations, having melting-point 240 to 242° C. The residual 250 c c specimen from which the ether-soluble porphyrin had been removed still showed distinct absorption bands. It was filtered through a column of Merck's alumina (*nach Brockmann*), but it was noticed that the porphyrin was much less firmly retained than is uroporphyrin, a broad zone of fluorescent material wandering fairly rapidly downwards. This behaviour, which was quite constant in all experiments with the ether-insoluble urinary pigment of the present case, rendered purification by chromatography difficult. When the pigment had reached the lower end of the column, the alumina was removed, dried, and boiled with anhydrous methyl alcohol containing 2 per cent of sulphuric acid. The resulting ester fraction which dissolved in chloroform was very dark in colour. It was shaken with 1 per cent hydrochloric acid which removed the porphyrin ester in fairly pure condition, but attempts to obtain a crystalline product after retransference to chloroform, &c, were not successful. The ester displayed an even greater solubility in methyl alcohol than uroporphyrin III ester, and the amorphous precipitates obtained by adding boiling methyl alcohol to concentrated solutions in chloroform were surmounted by intensely coloured mother liquors.

Attempted isolation using ethyl acetate. Preliminary tests having indicated that the ether-insoluble porphyrin was very sparingly extracted by ethyl acetate from solutions at pH 3.0, an attempt was made to recover in this way sufficient pigment for identification. Seven litres of urine, from which all ether-soluble porphyrin had been removed, were adjusted to pH 3.0 and subjected to continuous extraction by ethyl acetate. When the greater proportion had been extracted, the ethyl acetate solution was evaporated to dryness and the residue treated with methyl alcoholic hydrochloric acid. The ester fraction was passed into chloroform and it was noticed that a considerable amount of amorphous material having the two-banded spectrum of a porphyrin metal complex separated at the chloroform-aqueous methyl alcoholic interface. Moreover a pronounced instability of the porphyrin ester was also encountered and this proved to be another troublesome feature which dogged all efforts at purification during the course of the work. From the chloroform layer, a porphyrin ester was eventually obtained substantially free from other pigments, but all efforts to crystallize it resulted only in amorphous material. The absorption spectrum was measured in chloroform using a Hartridge reversion spectroscope, with the result shown in Table III. The figures for coproporphyrin tetramethyl ester and uroporphyrin octamethyl ester, as recorded by Schumm (1927), are reproduced for comparison.

Other methods of attempted isolation. Numerous devices were used in attempts to isolate the ether-insoluble porphyrin in a state of purity, but since all of these failed they will not be described in detail. Among the adsorbents used may be

the faecal porphyrin has been very much less in amount than was the case during the remissions of 1941 and 1942. It has not been possible to determine accurately the porphyrin excretion over a period of days at the present time, but qualitative examination suggests that the faecal porphyrin excretion is now of the order of only about a milligram per diem.

Special Chemical Examination of the Urine

The urine passed during periods of attack was generally dark brown, the colour resembling that of dark sherry. Spectroscopic examination usually

TABLE II

Approximate Pigment Balance

<i>Urine</i>	<i>Between Attacks</i>	<i>During Attacks</i>
Coproporphyrin	0.041 to 0.055 mg per diem	Approx 6 mg per diem
Ether-insoluble porphyrin	None detected	At least 6 mg per diem
Urobilin and urobilinogen	<1 mg per diem	11.4 mg per diem
<i>Faeces</i>		
Total other soluble porphyrin	39 mg per diem	<1 mg per diem
Stercobilin and stercobilinogen	54 mg per diem	8.0 mg per diem
Serum porphyrin	None detected	Approx 1 mg per 100 c.c. (mainly ether insoluble)
Blister fluid		Approx 0.1 mg per 100 c.c.
Bile	1.92 mg per 100 c.c.	

revealed a four-banded spectrum, but at times a two-banded spectrum was seen suggestive of metallo-porphyrin, thus

Specimen A Bands at 615, 570, 538, approx 500 m μ

Specimen B Bands at 570 and 540 m μ

The Ehrlich aldehyde test was usually positive, as was also the Schlesinger test for urobilin. Both ether-soluble and ether-insoluble porphyrins appeared to be present, among the former coproporphyrin III together with much smaller quantities of coproporphyrin I being identified by melting-points of the respective esters. All efforts to identify the ether-insoluble porphyrin or to obtain its methyl ester in pure crystalline condition have failed, notwithstanding repeated attempts made with large quantities of material. This porphyrin possesses characteristics, to be detailed below, which lead us to consider that it is neither uroporphyrin I nor III, nor a mixture of these two isomers. In particular, decarboxylation followed a course quite different from that characteristic of the uroporphyrins.

Examination of Specimen A This was a 24-hour specimen passed on 7.8.41, during a severe attack. An aliquot portion of 250 c.c. was acidified with acetic acid and extracted with ether and the porphyrin transferred, after washing, to dilute hydrochloric acid. Quantitative determination gave 3.35 mg per litre of urine. The porphyrin was purified by repeated transference between dilute acid and ether and esterified in the usual manner. The ester was almost completely soluble in cold, dry ether and crystallized from this solvent in aggregates

peratures above 135 to 140° C complete decolorization took place, but below this little change appeared to be suffered by the porphyrin, for on opening the tube and examining the contents only traces of the pigment could be extracted by the acetic acid-ether technique. Such amounts were too small for identification.

Special Chemical Examination of the Faeces

Owing to war conditions there was no opportunity of isolating the faecal porphyrin from the case until 1946, at which time the output of faecal coproporphyrin was very much less than during the acute phases of the disease. A portion of wet stool weighing 63 gm was extracted with acetic acid and ether in a proportion of 1 to 20. The extraction was repeated until the ether extracts were no longer coloured. After washing with water, the ether extract was then extracted with successive small quantities of 5 per cent hydrochloric acid. The extract thus obtained was neutralized with potassium acetate and again extracted exhaustively with ether. The ether extract was washed with dilute potassium acetate and then with water and evaporated to dryness *in vacuo*. The residue was taken up in methyl alcohol saturated with hydrochloric acid and left overnight. It was then diluted with 20 times its volume of ice-water and extracted with chloroform. The chloroform extract was then washed twice with water, once with dilute ammonia and twice more with water before filtration through a chloroform-moistened paper and evaporation to dryness. The crude material obtained weighed about 5 mg. This material was taken up in benzene and passed through a column of alumina (2 × 12 cm). After development with pure benzene, the column was allowed to dry and the three bands obtained separated mechanically and eluted with chloroform. The top band was brown in colour and was discarded. The next lower band appeared to be a porphyrin, but was too small in amount for identification to be possible. The third band after elution with chloroform yielded coproporphyrin I methyl ester. After recrystallization from chloroform and methyl alcohol, this ester softened at 240° and melted at 253.5° C. The yield was only a fraction of a milligram. The mother liquors were intensely coloured and behaved as if they contained considerable coproporphyrin III methyl ester, but this was not obtainable in a crystalline state. No uroporphyrin could be detected in the ether-acetic acid extracted faecal residue.

Special Chemical Examination of Blood

Serum (192 c c) of blood taken during an attack was shaken with acetic acid (one volume) and ether (two volumes). The top layer showed slight red fluorescence and the bottom layer intense deep red fluorescence, that is, the major part of the porphyrin was ether-insoluble. Attempts to isolate the ether-insoluble fraction failed. The ether layer was worked up in the usual way (see below). The water washings of the ether layer had a red fluorescence which did not pass into ether, but which could be taken out into ethyl acetate after

mentioned calcium phosphate or barium sulphate precipitated in the solution. The latter was particularly efficacious in concentrating the pigment from large volumes of urine, but after elution from the adsorbent by dilute sodium hydroxide, ammonia, or sodium phosphate solutions and adjustment of the reaction, no pH could be found at which precipitation of the pigment took place. The alkaline spectrum changed to the acid spectrum at about pH 3.0 to 3.5, but even

TABLE III

Absorption Spectra of Methyl Esters in Chloroform

<i>Ether-insoluble porphyrin from present case</i>	<i>Coproporphyrin</i>	<i>Uroporphyrin</i>
mμ	mμ	mμ
623.5	621.0	625.4
573.2	566.0	570.0
536.6	533.5	536.0
503.0	498.0	500.0

with preparations which had undergone a considerable degree of preliminary purification an iso-electric precipitation was not achieved. An investigation of the coproporphyrin content of the urine before and after acid hydrolysis, with the intention of discovering whether the ether-insoluble porphyrin was possibly a coproporphyrin-protein complex, led to an interesting result. There was no change in the coproporphyrin figures as a result of boiling the urine for two hours with one half of its volume of concentrated hydrochloric acid (that is, in about 10 to 11 per cent of hydrochloric acid), but a dark, amorphous humin-like precipitate was formed on to which all the porphyrins present were adsorbed. Performing the hydrolysis on a urine specimen from which coproporphyrins had been removed afforded a precipitate containing the ether-insoluble porphyrin. The precipitate was washed, dried, and treated with methyl-alcoholic hydrochloric acid, and the porphyrin ester separated by chloroform from the black amorphous material. Even such comparatively clean preparations failed to crystallize and behaved in the same intractable manner as the substance previously described.

Decarboxylation of the ether-insoluble porphyrin. Uroporphyrins I and III are readily decarboxylated by heating their methyl esters, suspended in 1 per cent. hydrochloric acid, in sealed tubes to 180 to 190° C, the corresponding coproporphyrins being produced in comparatively good yield. Since the coproporphyrins, being ether-soluble, are much more easily purified than the ether-insoluble uroporphyrins, attempts were made to decarboxylate the amorphous preparations obtained from the urine of our case with a view to identification of any coproporphyrins formed. The first experiments were carried out at a temperature of 180 to 185° C, but complete destruction took place, the tube containing a colourless liquid in which some greenish-black material was suspended. A trial with uroporphyrin III proved that the conditions were correct for the decarboxylation of this pigment. Heating was next carried out at lower temperatures, the sealed tubes being immersed in an open oil-bath so that the alterations in colour of the solution could be noted. It was found that at tem-

TABLE IV

Previously Described Cases of Chronic Porphyria Associated with Sensitivity to Light and with Abdominal Colic

<i>Authors</i>	<i>Pigmentation</i>	<i>Sensitivity to light</i> (Erythema and bullae)	<i>Constipation</i>	<i>Colic</i>	<i>Urine</i>	<i>Serum</i>	<i>Faeces</i>	<i>Special features</i>
Gotttron and Ellinger (1931)	+	+	+	+	Porphyrin	?	Dark	Originally diagnosed as erysipelas, neurotic features, muscle pain + Galactose test positive
Urbach and Blöchl (1934)	+	+	?	+	Coproporphyrin + + +, uroporphyrin + + (said to be uroporphyrin III) Waldenström (1937)	?	?	
Hoerberger and Schulze (1937)	+	+	?	+	Coproporphyrin III +, uroporphyrin I + + +	0	Porphyrin + + +	No sensitivity to ultra-violet light, severe liver change +, post mortem—partial yellow atrophy
van den Bergh and Grotpass (1937) Grotpass and Delfalque (1938)	?	+	?	+	No excess of porphyrin	+	Coproporphyrin I + + +, coproporphyrin III, mesoporphyrin, protoporphyrin	
Nesbitt and Watkins (1942), Berg (1946)	+	+	?	+	Coproporphyrin, uroporphyrin (as zinc complex)	+	?	Severely jaundiced, nervous symptoms +, died of bulbar paralysis, post mortem—liver degeneration
Merkelbach (1943)	+	+	+	+	Coproporphyrin I, other insoluble porphyrin not identified	?	?	
Taylor, Solomon, Weiland, and Figo (1946), Lanus, Solomon, and Figo (1947)	+	+	?	+	Coproporphyrin I, coproporphyrin III, no evidence of uroporphyrin	?	?	The patient was delivered of a male child, whose urine contained porphyrin during the first three days of life. The mother's milk also contained porphyrin

adjustment of the solution to pH 3. On shaking the ethyl acetate layer with 5 per cent hydrochloric acid, the latter developed a fairly intense red fluorescence. This behaviour is reminiscent of that of Waldenström's uroporphyrin III. The washed ether, which still fluoresced, was shaken with 5 per cent hydrochloric acid, and then the acid layer shaken with chloroform. No porphyrin passed into the chloroform. After retransference from acid to ether a typical porphyrin spectrum was shown by the hand spectroscope. It was therefore concluded that although some coproporphyrin was present, most of the serum-porphyrin was ether-insoluble.

The red cells were lysed with ether, ground with acetic acid, and extracted with ethyl acetate. After washing and transference to 5 per cent hydrochloric acid, a faint red fluorescence was obtained. The fluorescent material was not soluble in chloroform and was therefore probably coproporphyrin.

Discussion

There is little doubt that from the clinical point of view the present case is to be regarded as of the type previously described as chronic porphyria or porphyria cutanea tarda. Attacks of abdominal pain referable to the porphyria do not occur in the classical cases of so-called congenital porphyria described in the literature (Turner and Obermeyer, 1938), on the other hand, light sensitivity is not present in typical cases of acute porphyria. Various authors have described a form of chronic porphyria associated both with light sensitivity and abdominal symptoms, but a survey of the relevant literature suggests that such cases are rarer than recent reviews on the subject would suggest. Table IV summarizes the clinical and biochemical features of the recorded cases of this type. Several cases which have been described as cases of chronic porphyria were examples of long-standing congenital porphyria with light sensitivity but no abdominal symptoms, while on the other hand, some typical cases of acute porphyria have been termed chronic porphyria because the excess porphyrin excretion in the urine continued between the acute episodes of the disease. Such cases have not been included in Table IV. Our own case most resembles that described by Taylor, Solomon, Weiland, and Figge (1946) in which the earliest symptom was itching of the skin followed by the appearance of vesicles. Three months later an abdominal episode was ushered in, as in our case, by urgency and frequency of micturition. Despite a successful pregnancy, there had been no recurrence of the abdominal episode when the case was prepared for publication in August 1946 (Linás, Solomon, and Figge, 1947). The term chronic porphyria is not a good one, since all cases of congenital porphyria are chronic in nature, and so-called acute porphyria is almost certainly a chronic disorder associated with acute episodes. Waldenström's porphyria cutanea tarda is an equally unsatisfactory term since, while it is true that the cutaneous manifestations are late in appearing, the term does not indicate the abdominal symptoms which are so characteristic of the form of porphyria under discussion. From the chemical point of view, previous workers have found little characteristic of the condition. In most cases coproporphyrin III has been present in

function The amounts of porphyrin excreted in the urine during the attack were far greater than those hitherto encountered in patients with hepatic dysfunction, nor has there been described the excretion in such cases of such large amounts of ether-insoluble porphyrin as were excreted in the present case However, it is difficult to decide whether the hepatitis was an essential feature of the porphyria or whether the patient was suffering from a latent porphyria as manifest by the excessive amounts of porphyrin excreted in his faeces, and that during 1941 to 1943 several attacks of acute hepatitis resulted in diversion of pigment excretion from the faeces to the urine Whatever the primary mechanism, this diversion of excretion of pigments from the faeces to the urine was a prominent feature in our case

It would appear that this patient regularly excreted an excess of coproporphyrins I and probably III in the stools Such faecal excretion is in 1947 considerably less than was the case during the period 1940 to 1943 when the faecal excretion between abdominal attacks amounted to nearly 40 mg per diem At such times there was usually a normal amount of porphyrin in the urine Analysis of the bile suggested that most, if not all, of the faecal porphyrin was probably excreted by the liver During the attacks of jaundice this biliary excretion must have been greatly reduced and the pigments must have been diverted to the blood-stream and so to the kidneys and urine in a manner similar to that by which bilirubin is diverted to the same route in hepatogenous jaundice This is specially likely in view of the large amounts of porphyrin present in the blood-stream at such times There would then be maximum photosensitivity and abdominal pain caused by spasm of the gut At other times the diversion of pigment from the faeces to the urine would be less complete and any manifestation of the condition would presumably be confined to photosensitivity Since no ether-insoluble porphyrin could be demonstrated in the faeces, such a mechanism might imply a partial conversion of coproporphyrin to an ether-insoluble porphyrin, a process possibly involving carboxylation, and not improbable on chemical grounds provided that porphyrins of the same isomeric series were excreted in faeces and in urines Coproporphyrin I was isolated from the faeces passed in the remission period, but there was evidence that coproporphyrin III was also present in considerable amount, although it could not be isolated The urine contained mainly coproporphyrin III with some coproporphyrin I, together with an unidentified ether-insoluble porphyrin An alternative mechanism could be that the production of an ether-insoluble porphyrin by the body was an effective agent in producing the liver dysfunction with its consequent diversion of the coproporphyrins from the biliary tract-intestinal route of excretion to the urinary route There is no evidence to decide which of these mechanisms was effective in the present case It is well recognized that in many cases of acute porphyria, the porphyrin is excreted in the urine in the form of a precursor, porphobilinogen, or in the form of a metal complex, but it is not yet known whether these are the agents responsible for the various manifestations of the condition It is therefore of interest that the serum contained porphyrin and that the urine contained preformed

the urine, sometimes with small amounts of coproporphyrin I. Uroporphyrin I and III have been obtained sometimes separately and sometimes together in the urine. The faeces were not always examined, but in those that were, coproporphyrin III has been usually present, sometimes associated with coproporphyrin I. Grottepass and Delfalque (1938) reported protoporphyrin 9 and mesoporphyrin in the faeces of their patient, but these may well have been derived from dietary haem derivatives. Many of these findings may clearly require reconsideration in the light of recent work by Grinstein, Schwartz, and Watson (1945) and Watson, Schwartz, and Hawkinson (1945), who have found that uroporphyrin III, as isolated from the urine of many cases of acute porphyria, is not an entity, but is resolvable by chromatography into uroporphyrin I and a heptacarboxylic porphyrin of a type not previously described. If this work is confirmed the chemical work on the chronic porphyrias will clearly need to be reinvestigated and the whole conception of the classification of the porphyrias into a congenital form associated with the excretion of uroporphyrin mainly of series I and an acute form associated with the excretion of uroporphyrin mainly of series III will need revision. Unfortunately no conclusion is possible concerning the nature of the ether-insoluble porphyrin present in our case. All that can be said is that in some respects it showed similarity to Waldenström's uroporphyrin III, but in others differed sharply from the latter. The number of carboxyl groups cannot be stated. Its extreme lability tempts one to speculate that a vinyl group might be present in a side chain (cf. the lability of protoporphyrin).

Although an association between porphyria and jaundice has long been recognized, the earlier reports are difficult to evaluate because of an inadequate distinction between porphyria and simple symptomatic porphyrinuria associated with liver disease (that is independent of any family predisposition). Althausen (1931) and Urbach and Blöch (1934) concluded that hepatic dysfunction was present in cases of porphyria, but their methods of investigation were not those which have stood the test of time. Further confusion has arisen from the fact that in some cases liver function has been presumed impaired on account of a positive Ehrlich reaction with the urine. Such positive reactions may be given by urinary stercobilinogen or by porphobilinogen, the colourless precursor of uroporphyrin (Waldenström and Vahlquist, 1939). In our case, stercobilinogen itself was known to be present since it was estimated by Watson's (1937) method involving extraction with petroleum ether, a procedure which does not extract porphobilinogen. Nesbitt and Watkins (1942) described a case with photosensitivity, abdominal pain, nausea, and vomiting in which severe jaundice subsequently developed. Large amounts of coproporphyrin were isolated from the urine, while porphyrin, only some of which was ether-soluble, was present in the blood-serum. To our knowledge no case has been previously reported showing such a remarkable association of abdominal attacks and increased excretion of porphyrin in the urine with recurrent attacks of jaundice. Although there is little doubt that the attacks of jaundice were hepatogenous in nature, it is very unlikely that the porphyrin excretion was secondary to hepatic dys-

function The amounts of porphyrin excreted in the urine during the attack were far greater than those hitherto encountered in patients with hepatic dysfunction, nor has there been described the excretion in such cases of such large amounts of ether-insoluble porphyrin as were excreted in the present case However, it is difficult to decide whether the hepatitis was an essential feature of the porphyria or whether the patient was suffering from a latent porphyria as manifest by the excessive amounts of porphyrin excreted in his faeces, and that during 1941 to 1943 several attacks of acute hepatitis resulted in diversion of pigment excretion from the faeces to the urine Whatever the primary mechanism, this diversion of excretion of pigments from the faeces to the urine was a prominent feature in our case

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porphyrin even when examined in the fresh condition. It is not known, however, whether porphobilinogen was ever present in our case, since at the times of jaundice the positive Ehrlich reaction given by the urine was known to be due at least in part to stercobilinogen. No specific tests were performed to determine whether a portion of the material responsible for the positive reaction was insoluble in organic solvents, in which porphobilinogen is insoluble. Much of the urinary porphyrin appeared to be present in the form of a metal complex.

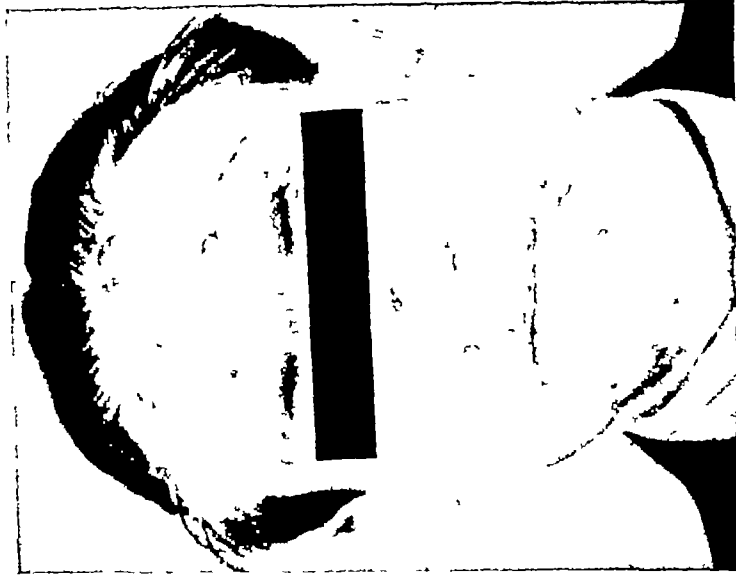
The remarkable change in nature of the photosensitivity is also worthy of comment. Combined sensitivity to light and trauma has been described by Schreus and Carrié (1931), while Blum (1941) emphasized that in hydroa and epidermolysis bullosa there was a sensitivity of the skin to trauma, whether porphyria was present or not, and suggested that the porphyrins might render damaged skin sensitive to light. It is difficult to explain the distinct phases of photosensitivity which were so evident in our own case. In one phase combined sensitivity to trauma and light was present, but there was no excess reaction after a trial exposure to ultra-violet light. Photosensitivity without undue reaction to ultra-violet light has been reported by Brunsting and Mason (1946). In the other phase, pure photosensitivity appeared to be present without the necessity for previous trauma. Unfortunately at this time the reaction to exposure to ultra-violet light was not investigated. It may well be that insufficient attention has in the past been paid to the spectral quality of the ultra-violet light used in such investigations.

Summary

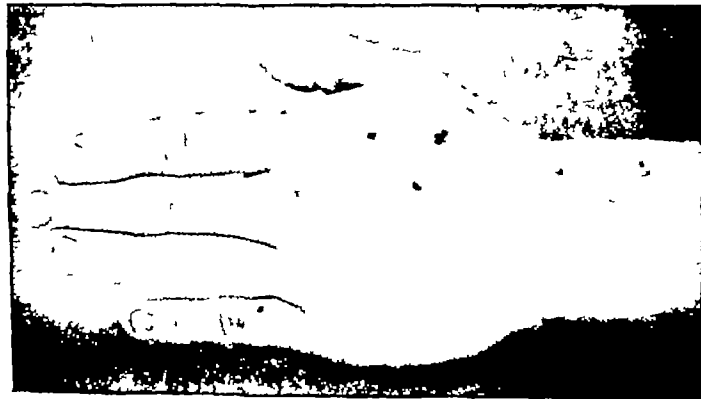
A case of chronic porphyria associated with recurrent jaundice is described. A preliminary phase of increased sensitivity to light was succeeded by a phase in which this manifestation was accompanied by recurrent attacks of abdominal pain usually associated with jaundice. The sensitivity to light subsequently diminished considerably and the abdominal attacks became less severe so that at the time of writing the patient is almost symptomless. During the active phases of the disease, large amounts of porphyrins were excreted via the kidneys and liver into the gut, the latter providing the major route of excretion when jaundice was not present and there was no abdominal pain. At times of jaundice and abdominal pain, the porphyrins together with the bile pigments were diverted via the blood-stream and kidneys to the urine. Coproporphyrin I was isolated from the faeces as the tetramethyl ester, but there was evidence that considerable amounts of coproporphyrin III were also present, although this could not be isolated. From urine passed during attacks of abdominal pain, considerable amounts of coproporphyrin III were isolated together with smaller amounts of coproporphyrin I. There was evidence of the presence also in the urine of an ether-insoluble porphyrin which despite all attempts at purification could not be induced to give a crystalline methyl ester. This porphyrin was more labile than uroporphyrin and was destroyed on heating to 180° C with 1 per cent hydrochloric acid, under which conditions the uroporphyrins are readily decarboxylated, giving coproporphyrins.

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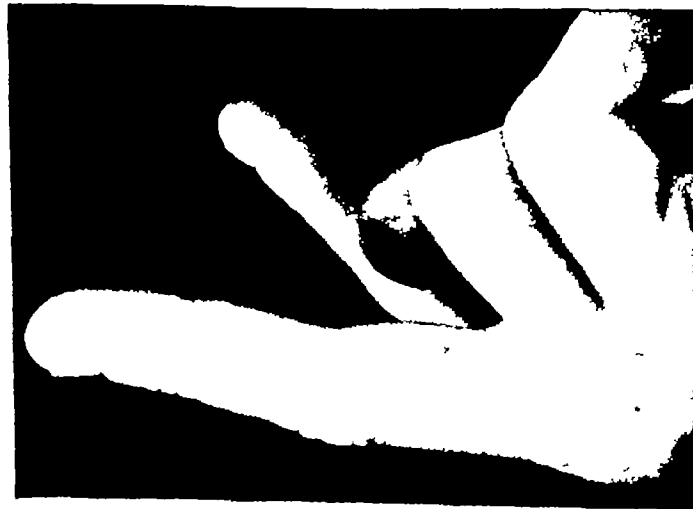
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Lesions of face (1941)



Lesions of hand (1941)



Traumatic lesion of hand (1012)

DOES SODIUM SALICYLATE CURE RHEUMATIC FEVER?¹

By JAMES REID

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THE exact place of sodium salicylate in the treatment of rheumatic fever is still uncertain. Some consider that the drug only relieves symptoms, while others claim that it also has a definite curative action in the disease. Clinical experience would certainly justify some hesitancy in attributing properties to it other than the well-established analgesic and antipyretic effects, firstly, because the time required for cure with oral administration is so extremely variable, and secondly, because relapses occur even while full doses of the drug are being taken. In spite of these objections, the older belief that sodium salicylate really does influence rheumatic inflammatory reactions has recently been revived, and it has even been suggested that organic heart disease may be prevented if the drug is given by intravenous infusion so that a high plasma concentration of salicylate is maintained throughout the active phase of the disease (Coburn, 1943). The striking point about Coburn's results was the comparatively short time required for cure of all patients treated by intravenous infusions of sodium salicylate. The remarkable uniformity of these results might have been partly due to the similarity in age and sex of the patients, but the method of giving salicylate was more likely to have been responsible. The second view, if true and confirmed, would imply that the usual practice of giving sodium salicylate by mouth is inferior to intravenous infusion, and if cure of rheumatic fever really depends on the concentration of salicylate in plasma it is conceivable that the variable results of treatment with sodium salicylate by mouth may be attributed to failure in attaining or maintaining sufficiently high plasma-salicylate levels in all patients treated in this way. We have investigated this possibility by estimation of plasma and urinary salicylate levels of patients with rheumatic fever, firstly, to define the variation in the levels encountered in a group of patients to whom the same doses of the drug were given by mouth, and secondly, to examine the relation of these levels to the disappearance of joint pains, fever, and tachycardia, and to the final cure of the disease as judged by the return of the erythrocyte sedimentation rate to normal. In this way it was hoped to decide whether sodium salicylate had curative in addition to analgesic and antipyretic properties.

Clinical Material and Methods

Twelve patients with rheumatic fever have been studied. Nine were adults and three were children. The ages of the adults ranged from 19 to 46 years and all had polyarthritides, fever, tachycardia, and a raised erythrocyte sedimentation

¹ Received December 27, 1947.

rate when admitted to hospital. The three children were 9, 12, and 14 years old and each had pericarditis, fever, and tachycardia on arrival in hospital. All patients were treated with sodium salicylate by mouth. Seven of the nine adults were given 2 gm sodium salicylate and 2 gm sodium bicarbonate at 6 a.m., 10 a.m., 2 p.m., 6 p.m., and 10 p.m. each day until complete recovery, as indicated by the return of the erythrocyte sedimentation rate to normal. The other two adults were given 2 gm sodium salicylate alone at the same times. Two of the children were given $1\frac{1}{2}$ gm sodium salicylate and $1\frac{1}{2}$ gm sodium bicarbonate, and the third child was given $1\frac{1}{2}$ gm sodium salicylate alone at the times specified. Blood for determination of the erythrocyte sedimentation rate and plasma-salicylate was collected in paraffined tubes containing sodium oxalate immediately before the 10 a.m. dose every day for about the first week of the treatment and thereafter three times weekly. The total volume of urine passed each day was also collected for estimation of urinary excretion of salicylate.

Plasma and urinary salicylate levels were determined by a method incorporating the extraction principles of Brodie, Udenfriend, and Coburn (1944) and the colour reaction of Jorissen described by Sherman and Gross (1911). Briefly the technique is as follows. Plasma or urine, acidified to pH 2, is extracted with iso-amyl alcohol in a glass-stoppered extraction bottle. The amyl alcohol containing the salicylate is separated by centrifugation, and an aliquot part shaken with a buffer at pH 8.6 to remove the salicylate. The two phases are again separated and the amount of salicylate in the buffer is estimated colorimetrically by the development of a red colour on boiling with copper sulphate in acetic acid and sodium nitrite. The method estimates total salicylate in both plasma and urine. Plasma from healthy subjects gives negligible 'blanks', but normal urine may give 'blanks' up to an equivalent of about 5 mg per 100 c.c. sodium salicylate. This amount is, however, very small in comparison with the large quantity of the drug excreted in the urine during treatment with sodium salicylate.

The erythrocyte sedimentation rate was employed as the best available indication of the duration of rheumatic activity. Though not a specific test it gives a fairly reliable index of the clinical state of the rheumatic patient, except in congestive cardiac failure when it is abnormally low and in anaemia when it is too high. As both these fallacies may be checked, the chances of misrepresenting the true state of a patient are small. The test was determined in Westergren tubes with the same specimen of oxalated blood that was used for the plasma-salicylate estimation. The erythrocyte sedimentation rate with oxalated blood was found to be faster than with citrated blood. The normal upper limit for oxalated blood was about 20 mm per hour as compared with 10 mm per hour for citrated blood.

Results

Plasma and urinary salicylate levels after oral dosage. The plasma and urinary salicylate levels of the seven adult patients who were given 2 gm sodium salicy-

late and 2 gm sodium bicarbonate five times daily by mouth progressively increased to reach peak levels in three to eight days, which ranged from 20 to 46 mg per 100 c c for plasma and 303 to 588 mg per 100 c c for urine. Patients with high plasma-salicylate levels had at the same time high urinary levels of the drug and conversely, patients with low plasma levels had low urinary levels. After the peak values had been reached the plasma and urinary salicylate levels simultaneously and unexpectedly began to fall. The falls were progressive, being moderate in some patients but pronounced in others. The lowest values of the whole group during the first three weeks of treatment ranged from 11 to 31 mg per 100 c c for plasma-salicylate, and 183 to 257 mg per 100 c c for urinary salicylate. In some patients the fall in urinary salicylate concentration was much more pronounced than the fall in plasma level of the drug, but this was found to be mainly due to a diuresis, as the total amount of salicylate excreted in the urine was not proportionately reduced. The changes in plasma and urinary salicylate of the three children were similar to those observed in the adults, except that the fall in the plasma levels of the drug tended to be more pronounced. An indication of the magnitude of the changes is given in Table I where the highest plasma and urinary salicylate levels of each patient are shown alongside the lowest recorded levels during the first three weeks of treatment.

TABLE I
Plasma and Urinary Salicylate and Oral Dosage

Patient	<i>Adults</i>			
	<i>Plasma-salicylate</i> (mg per 100 c c)		<i>Urinary salicylate</i> (mg per 100 c c)	
	Peak level	Lowest level	Peak level	Lowest level
McD	46	31		
W	42	19	588	237
D	40	25	420	149
McG	36	31	510	241
N	36	13		
P	26	16	324	257
C	20	11	303	183
	<i>Children</i>			
A W	33	16	451	138
J L	42	12		
M McP *	51	20	260	134

* Patient M McP was given $1\frac{1}{2}$ gm sodium salicylate five times daily without bicarbonate. The other two children received $1\frac{1}{2}$ gm sodium salicylate and $1\frac{1}{2}$ gm sodium bicarbonate five times daily. The adults all received 2 gm sodium salicylate and 2 gm sodium bicarbonate five times daily.

Two important conclusions may be drawn from these findings. Firstly, the variation in plasma and urinary salicylate levels of the adult patients who were all given the same dose of the drug is considerable, and secondly, both plasma and urinary salicylate levels tend to fall after the initial peak levels have been reached, in spite of continuous oral administration of the drug. The cause of the fall in plasma and urinary salicylate is not yet known, but it is interesting

to compare these observations with previous experiments (Reid, 1947) when salts of antimalarial bases were given by mouth for about the same periods and similar changes in the blood and urinary concentration of the drugs were

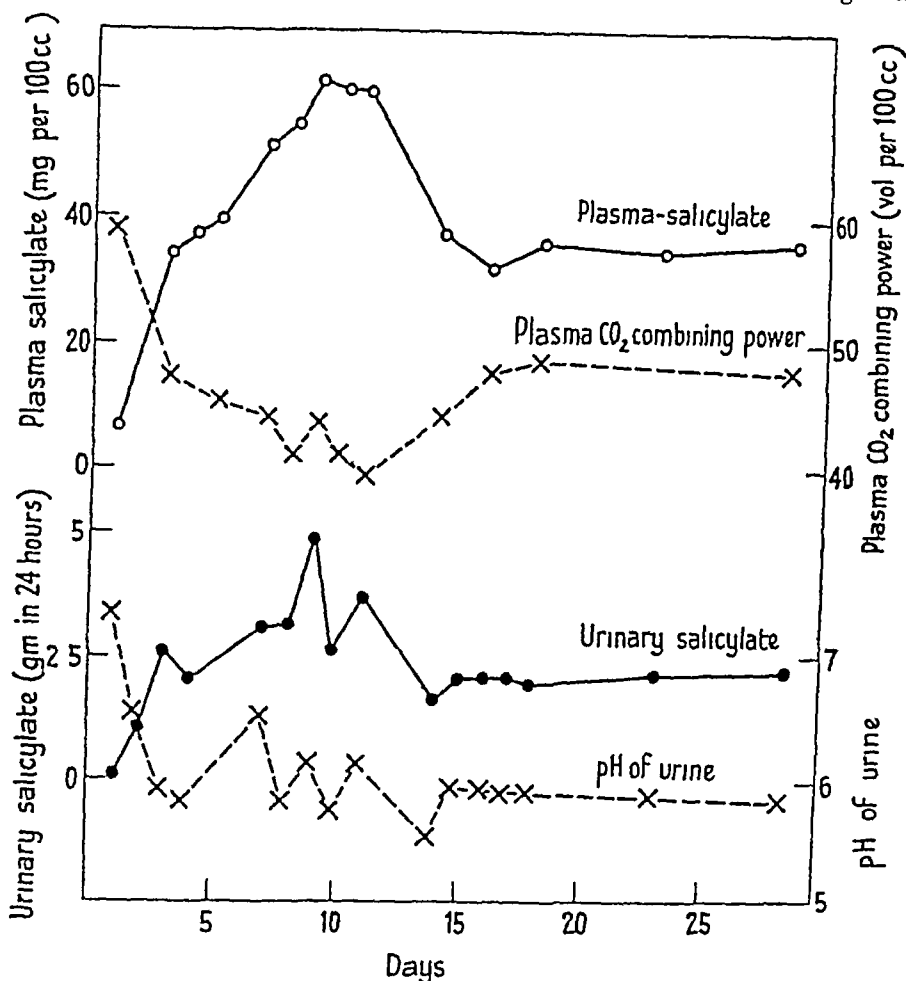


FIG 1 The inverse relationship between plasma salicylate and carbon dioxide combining power on the one hand and urinary salicylate and pH on the other is illustrated

observed. In the work with mepacrine, these changes were attributed to alterations in the acid-base balance of the body. It therefore seemed possible that the rise and fall in plasma and urinary salicylate might also be due to the same cause. This possibility has been explored and the relations of the alkali reserve and pH of the urine to the plasma and urinary levels of the drug examined in three adults with rheumatic fever who were treated with 2 gm sodium salicylate five times daily by mouth. One of the three patients had been treated previously, but had relapsed after salicylate treatment was stopped, the other two were new patients. Sodium bicarbonate was purposely omitted because it seemed advisable to observe the effect of sodium salicylate alone.

Acid-base balance and plasma and urinary salicylate levels The alkali reserve and pH of urine of the three patients who were given sodium salicylate alone showed essentially the same changes. When the plasma and urinary salicylate levels were rising to peak levels, the alkali reserve and urinary pH were falling to their lowest values. Conversely, when the plasma and urinary levels of the drug were falling the alkali reserve and urinary pH were rising. These changes in acid-base balance were also accompanied by alterations in urinary volume. When the alkali reserve and urinary pH were falling, the volume of urine was much smaller than when both were rising. The results, illustrated in Fig 1, indicate that a rise in plasma and urinary salicylate is associated with an acidosis, a fall in both levels of the drug with a change in the acid-base balance in the opposite direction. The plasma and urinary salicylate levels of the three adult patients who were treated with sodium salicylate alone differed from the levels of the other seven patients who were given the same dose of sodium salicylate along with sodium bicarbonate. The first three patients had higher plasma-salicylate levels but lower urinary levels of the drug than the seven patients who were also given sodium bicarbonate. Smull, Wégria, and Leland (1944) found that the administration of sodium bicarbonate depressed the plasma-salicylate level, and Coombs, Warren, and Higley (1945) suggested that this was due to increased urinary excretion of the drug. Our findings support this conclusion, and further confirmation was obtained by comparing the plasma and urinary salicylate levels of a patient whose initial attack of rheumatic fever was treated with sodium salicylate and sodium bicarbonate and whose first relapse was treated with the same dose of sodium salicylate alone. The plasma concentration of the drug in this patient was much lower, and the urinary concentration and total output of the drug were proportionately higher, when the sodium bicarbonate was given along with sodium salicylate (Fig 2). It therefore appears that the main action of sodium bicarbonate is to reduce the plasma level of salicylate by promoting the excretion of the drug in the urine in virtue of its effect on the acid-base balance of the body. The changes in plasma and urinary salicylate that have been described are scientifically interesting, but their practical importance depends on the effect that they may have in the treatment of rheumatic fever. The next step was therefore to investigate the relation of the plasma and urinary levels of the drug both to the relief of symptoms and the cure of a rheumatic attack.

Relief of symptoms in relation to plasma and urinary salicylate levels In five of the seven adult patients who were given 2 gm sodium salicylate and 2 gm sodium bicarbonate five times daily by mouth, joint pains, fever, and tachycardia had completely disappeared within four days of starting treatment, while the plasma and urinary salicylate levels were progressively rising to peak values of 36 to 46 mg per 100 c c for plasma and 420 to 678 mg per 100 c c for urine. Of the two remaining patients, one obtained some symptomatic relief, but slight joint pain on movement, mild fever, and tachycardia persisted for about 10 days, although the peak plasma and urinary salicylate levels were no higher than 26 mg and 375 mg per 100 c c respectively. The other patient had little or

no symptomatic relief, joint pain and swelling persisted more or less continuously throughout the first three weeks of treatment, and during this time the peak plasma-salicylate level was as low as 20 mg per 100 cc and the peak urinary level 303 mg per 100 cc. The dose of sodium salicylate and sodium bicarbonate given to this patient was then doubled and three days later all

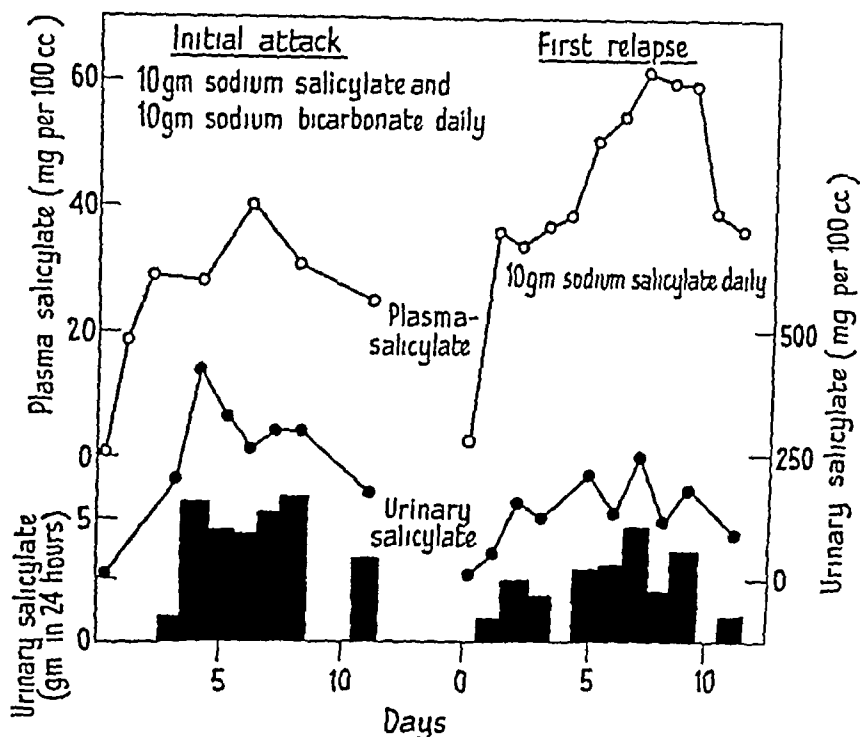


FIG 2 An initial attack of rheumatic fever was treated with 10 gm sodium salicylate and 10 gm sodium bicarbonate daily, and a subsequent relapse with 10 gm sodium salicylate alone. When sodium bicarbonate was given along with sodium salicylate the plasma level of the drug was much lower, but the urinary level and total output of the drug in urine were much higher than when sodium salicylate was given alone.

symptoms had disappeared, while the plasma and urinary salicylate levels had risen to secondary peak values of 33 mg and 618 mg per 100 cc respectively.

The results suggest that the disappearance of joint pain, fever, and tachycardia is related to the concentration of salicylate in plasma. Additional evidence in support of this conclusion was provided by two patients, one adult and one child, who both showed a pronounced fall in plasma-salicylate level after the peak value had been reached. The adult's symptoms were relieved within three days of starting treatment and in this time the plasma-salicylate level reached a peak of 36 mg per 100 cc. The level then gradually fell to 13 mg per 100 cc on the 12th day of continuous salicylate dosage, when a relapse occurred as indicated by the reappearance of joint pain, fever, and tachycardia. The clinical manifestations noted in association with the fluctuations in plasma-

salicylate level of the child were even more interesting. This child had pericardial friction, fever, and tachycardia when treatment was started with $1\frac{1}{2}$ gm sodium salicylate and $1\frac{1}{2}$ gm sodium bicarbonate five times daily by mouth. Two days later pericardial friction, fever, and tachycardia disappeared, while the plasma level of the drug was rising to reach a peak of 42 mg per 100 c c on

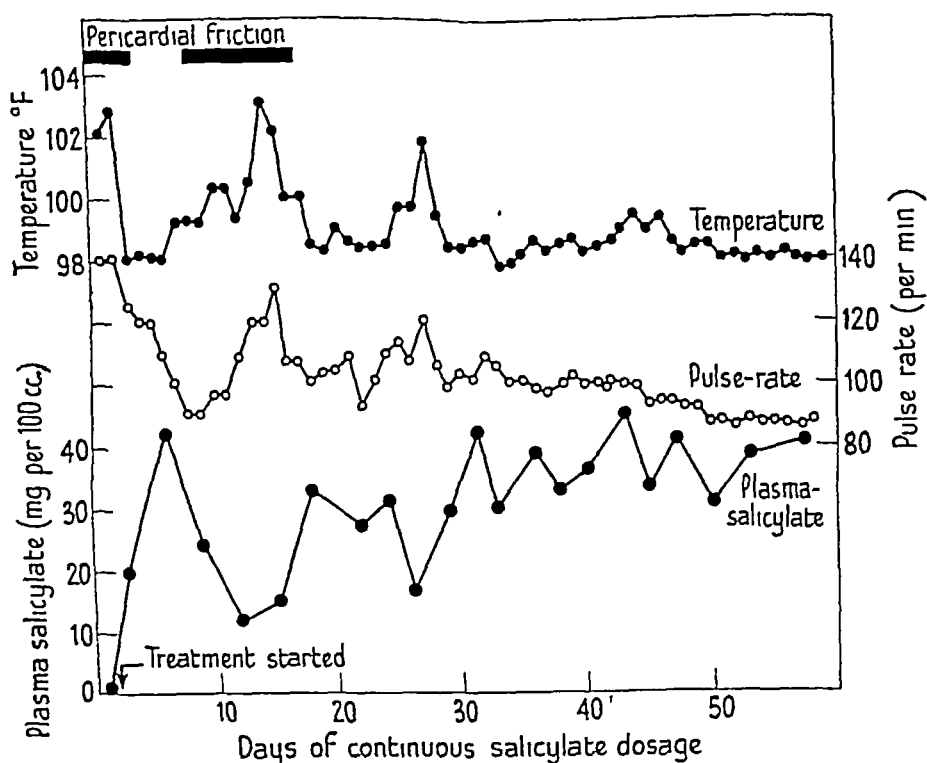


FIG 3 The relation between relapses and remissions of rheumatic fever and the plasma salicylate level is illustrated. Relapses as indicated by the return of fever and tachycardia coincide with a sharp fall in plasma salicylate level, remissions are associated with a rise in the plasma level of the drug.

the fourth day of treatment. The level then progressively fell to 12 mg per 100 c c on the 10th day in spite of continuous oral salicylate administration, and coinciding with this fall, pericardial friction and tachycardia reappeared. The plasma-salicylate again rose to 38 mg per 100 c c on the 17th day of salicylate dosage, and pericardial friction, fever, and tachycardia again disappeared. Another fall in the plasma-salicylate level to 16 mg per 100 c c on the 25th day of salicylate administration was associated with a smaller elevation of temperature and pulse-rate, but on this occasion pericardial friction did not return (Fig 3). This remarkable association between the disappearance and return of clinical manifestations of the disease on the one hand, and a rise and fall in the plasma-salicylate level on the other, suggests that relapses of rheumatic fever developing while sodium salicylate is continuously given by mouth are

due to failure to maintain an adequate concentration of salicylate in the plasma rather than to a loss of therapeutic activity of the drug

Cure of rheumatic fever in relation to plasma and urinary salicylate levels The return of the erythrocyte sedimentation rate to normal has been employed as the only available objective index to assess cure of an attack of rheumatic fever. An attempt to decide whether sodium salicylate really has curative properties in the disease has been made by examining the relation of the erythrocyte sedimentation rate to the plasma and urinary levels of the drug of the seven adult patients previously described. The erythrocyte sedimentation rates of the patients immediately before the treatment ranged from 95 to 122 mm in one hour, and after three weeks they were either approaching or had returned to normal in all but one patient. The fall in the erythrocyte sedimentation rate was progressive and in a graph more or less linear, and in order to compare one patient with another the rate of fall in erythrocyte sedimentation rate per diem was calculated over the period that plasma and urinary salicylate levels were estimated. The average plasma-salicylate level during the time that the erythrocyte sedimentation rate was falling was also calculated for each patient and compared with the average fall in erythrocyte sedimentation rate each day. The results are shown in Table II. It will be observed that the average plasma-

TABLE II

Plasma-salicylate and the erythrocyte sedimentation rate during the first three weeks of treatment

Patient	Plasma salicylate (mg per 100 c c)			Erythrocyte sedimentation rate (mm in one hour)		
	Peak level	Lowest level	Average level	Initial rate	Final rate	Average fall per diem
McG	36	31	34	95	10	6.0
McD	40	31	37	120	20	5.0
D	40	25	31	115	30	4.0
W	42	19	30	115	40	3.5
P	26	16	22	100	50	2.2
N	36	13	21	100	65	2.0
C (a)	21	11	17	122	125	0
C (b)*	33	22	28	100	20	4.2

* Patient C's erythrocyte sedimentation rate was practically unchanged during the first three weeks of treatment (a), but by doubling the dose of sodium salicylate and sodium bicarbonate it rapidly returned to normal (b).

salicylate values of the seven patients ranged from 17 to 37 mg per 100 c c, and the average fall in erythrocyte sedimentation rate each day was from 0 to 6 mm in one hour. When the average plasma-salicylate level was only 17 mg per 100 c c the erythrocyte sedimentation rate remained unchanged. When the average level was about 25 mg per 100 c c the erythrocyte sedimentation rate fell slowly, but when it was about 35 mg per 100 c c the erythrocyte sedimentation rate rapidly returned to normal. The remarkable consistency of the results suggest that a fall in the erythrocyte sedimentation rate may be directly related to the concentration of salicylate in plasma, and this suggestion is

supported by the series of events in a patient with an average plasma-salicylate level of only 17 mg per 100 c c, whose erythrocyte sedimentation rate remained unchanged during the first three weeks of treatment. When the average plasma-salicylate value of this patient was increased to 27 mg per 100 c c by doubling the dose of sodium salicylate and sodium bicarbonate, the erythrocyte sedimentation rate rapidly returned to normal (Table II). It therefore appears that cure of an attack of rheumatic fever, at least as indicated by the return of the erythrocyte sedimentation rate to normal, depends both on the attainment of a high plasma-salicylate level and on the maintenance of this level for so long as the disease can be presumed to be active either by the presence of symptoms or an elevated erythrocyte sedimentation rate.

In view of the close relationship that has been observed between plasma-salicylate level and the total output of the drug in the urine, it was not surprising to find that a rapid fall in erythrocyte sedimentation rate was also associated with a large total urinary excretion of the drug (Table III). It was, however,

TABLE III

Urinary salicylate and the erythrocyte sedimentation rate during the first three weeks of treatment

Patient	Urinary salicylate				Average fall in erythrocyte sedimentation rate each day (mm in one hour)
	Highest level (mg per 100 c c)	Total output (gm per diem)	Lowest level (mg per 100 c c)	Total output (gm per diem)	
McG	510	6.5	241	5.0	6.0
McD	420	5.7	149	4.2	4.0
W	588	5.0	237	3.7	3.5
P	324	4.8	257	5.1	2.2
C (a)	303	4.5	183	3.5	0
C (b)*	618	11.8	205	8.0	4.2

* Patient C's erythrocyte sedimentation rate was practically unchanged during the first three weeks of treatment (a), but by doubling the dose of sodium salicylate and sodium bicarbonate it rapidly returned to normal (b).

at first disconcerting to find that a rapid fall in erythrocyte sedimentation rate was also related to a progressive fall in urinary salicylate concentration, though there was only a slight reduction in the total output of the drug in the urine. The explanation of the steady fall in the urinary concentration of salicylate was soon shown to be the occurrence of a progressive diuresis, and the extent of the diuresis appeared to be inversely related to the fall in the erythrocyte sedimentation rate. The greater the diuresis, the more rapid the fall in the erythrocyte sedimentation rate. These findings are illustrated in Figs 4 and 5. In Fig 4 the complete results in one patient are shown. This patient failed to respond to 10 gm sodium salicylate and 10 gm sodium bicarbonate daily, but was later cured by doubling the dose of the drugs. While the erythrocyte sedimentation rate remained high for three weeks at about 120 mm in one hour, the plasma and urinary salicylate levels were fairly constant and the urinary volume tended to fall. After doubling the dose of drugs the plasma and

urinary salicylate levels rose quickly, the erythrocyte sedimentation rate rapidly returned to normal, and the urinary volume was greatly increased. In Fig 5, the results in two other patients are shown. One patient responded promptly

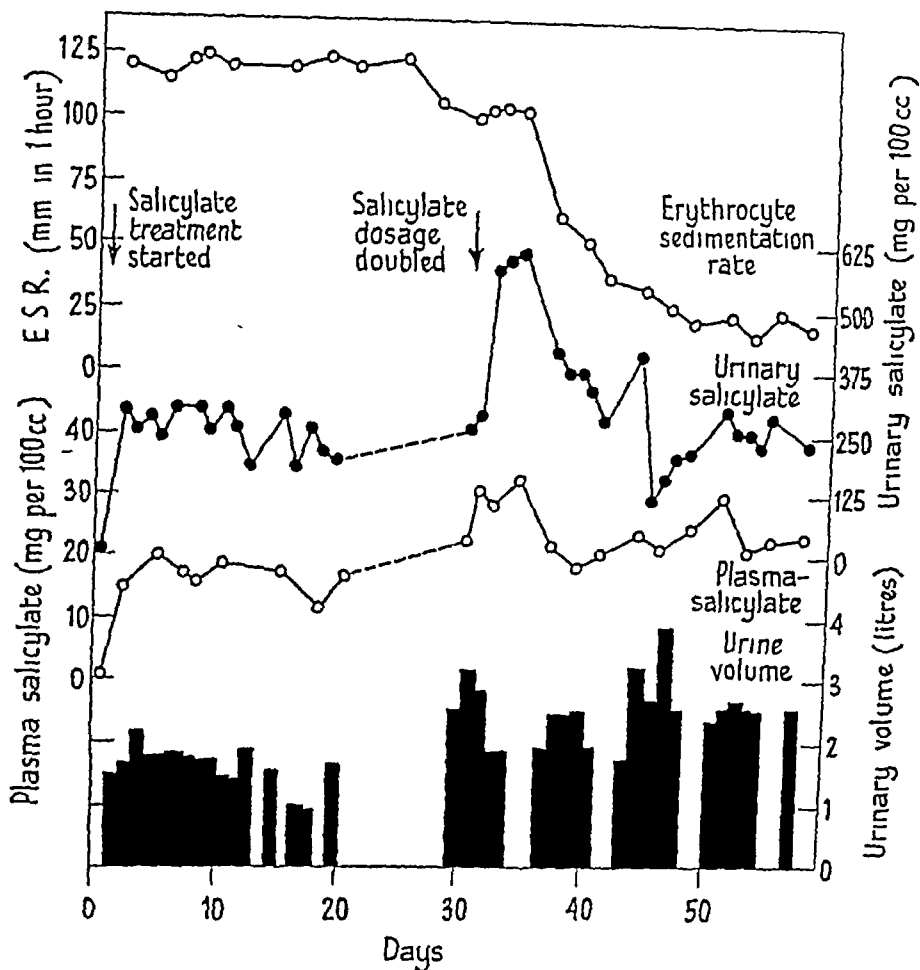


FIG 4 During the first three weeks of treatment with 10 gm sodium salicylate and 10 gm sodium bicarbonate daily the erythrocyte sedimentation rate remained unchanged, the plasma and urinary salicylate levels were low, and the urine volume fairly constant. On doubling the dose of the drugs the erythrocyte sedimentation rate rapidly returned to normal, and the plasma and urinary salicylate levels and urine volume increased.

to treatment, the other more slowly. The patient who responded quickly had a higher plasma-salicylate level, a higher peak urinary concentration of the drug, and a much sharper fall in the urinary salicylate concentration with a more pronounced diuresis. The significance of this diuresis is at present under investigation, it may be important therapeutically, but on the other hand it may simply be a side-effect of the drug. The practical importance of estimating the total urinary excretion of salicylate is that it gives a fairly reliable index of the plasma concentration of the drug. It may therefore provide a simple method

for controlling salicylate dosage in the treatment of the disease, since the technique is more easily carried out with urine than with plasma

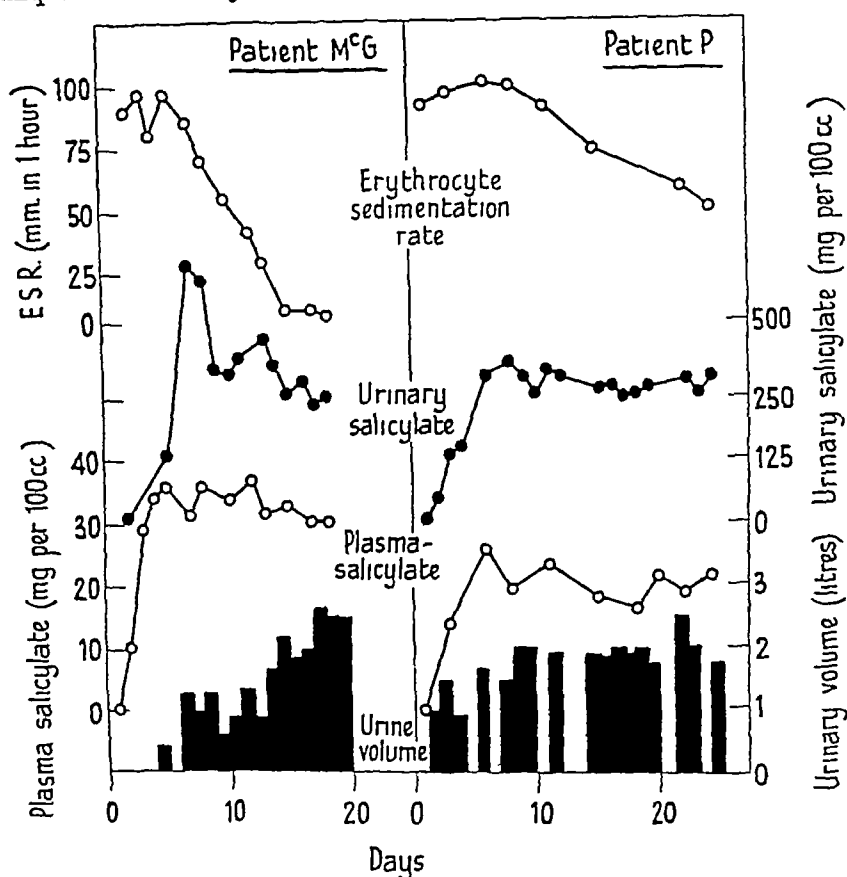


FIG 5 Two patients with rheumatic fever (McG and P) were treated with 10 gm sodium salicylate and 10 gm sodium bicarbonate daily. The erythrocyte sedimentation rate of one patient (McG) fell rapidly, that of the other patient (P) more slowly. The patient whose erythrocyte sedimentation rate fell rapidly had a higher plasma salicylate level, a higher urinary concentration, and a sharper fall in urinary salicylate concentration associated with a more pronounced diuresis.

Discussion

An attempt has been made to decide whether sodium salicylate has a curative action in rheumatic fever in addition to its well-recognized antipyretic and analgesic properties. The return of the erythrocyte sedimentation rate to normal was used as the index of cure of an attack of the disease, and its relation to the plasma and urinary level of the drug has been examined. The plasma-salicylate levels of the seven adult patients with rheumatic fever who were all treated with the same doses of sodium salicylate and sodium bicarbonate showed a wide range of variation. Likewise, the time required for cure of the patients varied within wide limits. The rate of fall in the erythrocyte sedimentation rate of

urinary salicylate levels rose quickly, the erythrocyte sedimentation rate rapidly returned to normal, and the urinary volume was greatly increased. In Fig 5, the results in two other patients are shown. One patient responded promptly

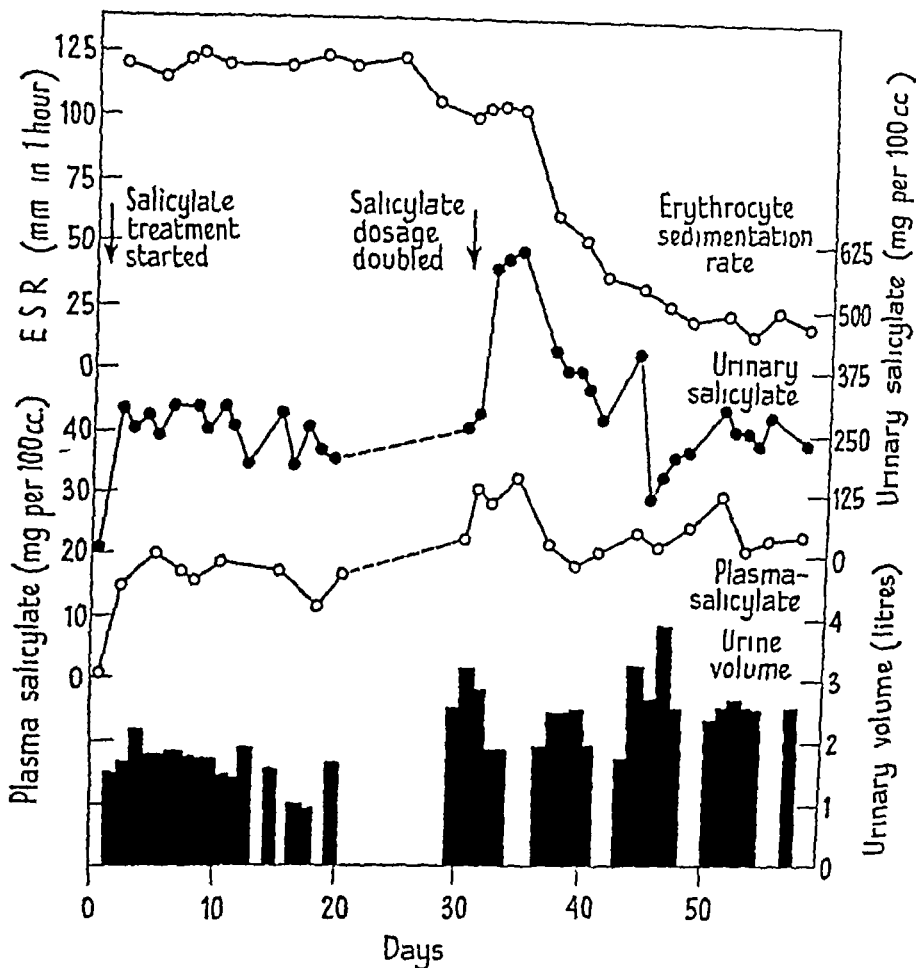


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oral administration of sodium salicylate can really cure the disease. The return of the erythrocyte sedimentation rate to normal was taken as the criterion of cure as being the best test at present available.

2 Cure appears to depend on reaching and maintaining a high plasma-salicylate level (between 30 and 40 mg per 100 c c) while the disease is still active.

3 Building up the plasma-salicylate level to an adequate peak value is easy with oral administration of the drug, but maintaining a high level is another matter, for after the peak value has been reached the level tends to fall in spite of continuous dosage. The fall is slight in some patients, but pronounced in others. It has been found to be associated with changes in acid-base balance of the body fluids.

4 This fall in plasma-salicylate level is of great practical importance, because relapses of the disease during oral administration of the drug develop when the fall is pronounced.

5 Completely effective treatment of rheumatic fever with salicylate seems to demand at present that dosage should be controlled by repeated plasma or urinary salicylate estimations, firstly, because cure of the disease depends not only on reaching but also on maintaining a high plasma-salicylate level, secondly, because the variation in plasma levels of patients receiving the same doses of the drug is great, and thirdly, because the initial peak is followed by a fall which in some patients may reach so low a level that a relapse will occur unless the dose of drug by mouth is increased at once.

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each patient, however, was found to depend on the average plasma level of the drug during the period when the disease was still active. When the average plasma level was less than 20 mg per 100 c c the erythrocyte sedimentation rate showed no sign of falling, when the level was between 20 and 30 mg per 100 c c a slow fall was observed, when it was between 30 and 40 mg per 100 c c the rate rapidly returned to normal. If the erythrocyte sedimentation rate is a reliable index of rheumatic activity, then sodium salicylate has a curative action in the disease directly related to the plasma concentration of the drug. This conclusion is strongly supported by the observation that recurrence of the disease during oral salicylate treatment coincides with a pronounced fall in plasma-salicylate level and subsequent remission with a secondary rise in the plasma level of the drug. The aim of treatment therefore appears to be to keep the plasma-salicylate level between 30 and 40 mg per 100 c c while the disease is active, but this is often difficult because the plasma level of the drug tends to fall in spite of full dosage after the initial peak has been reached. Investigations so far indicate that the cause of these fluctuations in plasma-salicylate level is an alteration in the acid-base balance of the body fluids. A rise in the plasma level of the drug is associated with a fall in alkali reserve and urinary pH, whereas a fall in plasma-salicylate is accompanied by a rise in alkali reserve and urinary pH. The cause of this rise in alkali reserve and urinary pH is still uncertain, but the observations suggest that sodium salicylate induces an acidosis which in time requires to be controlled by the usual well-known reaction of the body, namely, changes in respiration and increased production of base in the form of ammonia. The fall in the plasma level of the drug after the initial peak value has been reached is likely to be due to over-compensation of the acidosis. If this interpretation of the results of oral treatment proves to be correct then similar fluctuations in plasma-salicylate may be expected after intravenous administration of the drug, since it is the plasma-salicylate level that influences the changes in acid-base balance. The only real advantage that intravenous infusion may have over oral dosage is to ensure that patients quickly attain adequate therapeutic plasma levels of the drug, but this may be offset by technical difficulties in administration and specially by a greater incidence of serious toxic effects. The main practical problem in the treatment of rheumatic fever is to know when enough salicylate is being given, and the only reliable method of controlling dosage at present is by repeated estimations of the level of the drug in plasma or urine. The practice of giving large doses of salicylate until fever, tachycardia, and joint pains have been relieved and then drastically reducing the dose is condemned. It simply invites a relapse, since the reduction in dose is likely to coincide with the natural tendency of the plasma level of the drug to fall after the initial peak value has been reached.

Summary

1 Observations have been made on patients with rheumatic fever which strongly suggest that in addition to the well-known relief of symptoms, adequate

THE TOXIC MANIFESTATIONS OF SODIUM SALICYLATE THERAPY¹

By J. D. P. GRAHAM AND W. A. PARKER

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Sodium salicylate is widely used in the treatment of acute rheumatic fever and the more chronic forms of rheumatism. While there may be disagreement as to its precise value in the therapy of various rheumatic conditions, there is general agreement that it is a toxic substance giving rise to a variety of untoward and even alarming symptoms which may interfere with its administration. Since the days of Stricker (1876) many accounts have been given of various aspects of the toxicity of sodium salicylate, but only recently has it been possible to correlate the occurrence of individual symptoms with a precise knowledge of the level of salicylate in the blood-plasma of patients. Brodie, Udenfriend, and Coburn (1944) published details of a simple method of colorimetric estimation of plasma-salicylate which has brought a clarification of the position. Wégria and Smull (1945) stated that the toxic symptoms from sodium salicylate therapy were not marked until plasma levels were above 50 mg per 100 c.c. while Jager and Alway (1946) found no serious toxic symptoms with a plasma-salicylate level under 40 mg per 100 c.c., but noted that above this level hyperventilation tended to occur. Nausea, vomiting, and acniform skin eruptions appeared early, but resolved with continued therapy. Manchester (1946) ignored such transient symptoms as tinnitus, deafness, vertigo, and sweating, but was concerned over the appearance of dyspnoea, persistent vomiting, and delirium. Warren, Higley, and Coombs (1946) also stressed the onset of hyperventilation as a serious phenomenon. The tendency of recent years has been to push the dosage of sodium salicylate to the limits of tolerance in an endeavour to exert the maximum therapeutic effects as early as possible in the disease, and with this aim in view intravenous injection of salicylate has been reintroduced into hospital practice. If large doses of sodium salicylate are to be administered orally, rectally, or intravenously to patients, more accurate information about the occurrence and order of appearance of toxic manifestations seems desirable. Accordingly an endeavour has been made to assess the relationship between the occurrence of the various toxic effects of salicylate and the plasma level of the drug, and to investigate the cause and mechanism of production of the more serious common symptoms of overdosage, namely, persistent vomiting and hyperventilation. Observations have been made on 40 patients of both sexes and of varying ages receiving courses of salicylate

¹ Received November 3, 1947

THE TOXIC MANIFESTATIONS OF SODIUM SALICYLATE THERAPY¹

By J D P GRAHAM AND W A PARKER

(From the University Department of Materia Medica, and Stobhill Hospital, Glasgow)

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therapy for rheumatic diseases, acute and chronic. In addition a group of 30 non-rheumatic convalescents who served as controls was given similar doses of salicylate and observed.

The Relationship Between Plasma Concentration of Salicylate and its Toxic Effects

The salicylate concentration in the plasma of samples of venous blood was estimated whenever the patient initially experienced a recognizable toxic symptom from sodium salicylate therapy in the first seven days of treatment. Eighty-seven observations were made on 58 subjects, providing a representative selection of such complaints. The toxic manifestations encountered are shown in Table 1, in the ascending order of mean plasma-salicylate levels at which they first occurred. There is a variation in the levels at which individual toxic symptoms first were noted in different patients, but an orderly rise in plasma-salicylate concentration leading from the less to the more severe toxic effects was observed. Excluded from the table as due to idiosyncrasy was the appearance in three cases of tinnitus, deafness, and vomiting at a plasma-salicylate

TABLE I

Relationship of plasma level of salicylate to the toxic manifestations of sodium salicylate. The plasma level is shown on initial appearance during the first week of a toxic symptom on 87 occasions from 58 patients receiving sodium salicylate therapy.

Toxic manifestation noted	Number of observations made	Plasma-salicylate level at first appearance of sign (mg. per 100 c c)		
		Lowest	Highest	Mean
Erythema	3	12.2	26.4	19.5
Tinnitus	9	10	39.4	24.3
Deafness	9	10	48	25.5
Nausea	9	12.6	39.6	26.7
Vomiting	10	16.3	38.6	28.2
Albuminuria	4	25.2	41.6	32.1
Hyperventilation	10	21	44.2	32.8
Marked sweating	8	22.6	48	36.6
Headache	5	20.3	58.1	39.8
Vertigo	1	40		40
Severe drowsiness	1	36.6	42.5	40.4
Acetonuria	2	41.5	56	43.7
Haematuria	2	43.6	50	46.8
Confusion	4	41	53.6	46.9
Excitement, euphoria	2	42.5	53.6	48.1
Pulmonary oedema	1	49.4		49.4
Severe dyspnoea	3	46	53.6	50.9
Haemorrhage	1	51.8		51.8

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rheumatic fever This level was attained in 33 patients in our series, all of whom complained of tinnitus and deafness One-half were nauseated and one-third showed hyperventilation Analysis of the toxic manifestations observed is made in Table II A plasma-salicylate level of 35 mg per 100 c c occurring in the first seven days of salicylate therapy appears to be the point above which the more alarming toxic symptoms appear, and patients with plasma levels rising above this concentration should be watched most carefully for undesirable developments, plasma levels being checked frequently

TABLE II

The incidence of toxic manifestations in 33 patients whose plasma level rose above 35 mg. per 100 c c during the first seven days of salicylate therapy

<i>Toxic manifestations</i>	<i>Number of patients affected</i>	<i>Toxic manifestations</i>	<i>Number of patients affected</i>
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Marked sweating	4	Epistaxis	2
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Tinnitus, deafness, nausea, and vomiting Therapy was maintained despite the presence of these effects, which usually disappeared in a few days and did not recur with the subsequent attainment of much higher plasma-salicylate levels They were not considered to be of great significance and when troublesome were controlled by omitting the administration of salicylate for 24 to 48 hours

Persistent vomiting Vomiting on more than four occasions in one day was treated by omission of salicylate for 48 hours, after which it seldom recurred.

Severe sweating in the afebrile patient This toxic effect was common with all routes of administration, but did not necessitate interruption of therapy With intravenous salicylate therapy it occurred three to four hours after infusion had ceased and when peak plasma-salicylate levels had been passed

Skin troubles The onset of a drug rash, such as erythema of the face, neck, chest, and flexor aspects of the arms, within 24 hours of beginning salicylate therapy was held to be of no significance The rash faded with continued exhibition of the drug and there was no desquamation or residual discoloration Two cases of acniform eruption were seen in the third week of salicylate therapy when plasma levels had fallen from the high levels attained at the beginning of treatment The eruptions did not progress in severity and salicylate therapy was continued

Urinary abnormalities The occasional presence of red blood-cells in the urine and at other times the appearance of albumin (up to 1 gm per litre) disappeared with continued therapy and increased fluid intake They were regarded as of no significance Acetonuria was infrequent and occurred at plasma levels which

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were surpassed in other patients with marked toxic symptoms but without the appearance of this abnormality, it was associated with dehydration from sweating and vomiting. Myers and Ferguson (1929) have shown that with massive doses of salicylate, acetone does not appear in the blood. Anderson's (1945) report of frequent ketosis in children on prolonged salicylate therapy can be explained by the observations of Ergaman, Forbes, and Case (1947) that in salicylate poisoning dehydration is of rapid onset and frequent occurrence in children. The two patients observed by us with ketosis were treated with increased fluids by mouth which relieved the condition, and salicylate therapy was continued.

Headache, vertigo, and mental symptoms Headache tended to diminish with continued therapy, in one patient only was it severe and persistent. Drowsiness, confusion, excitement, and euphoria were noted in that order as plasma-salicylate levels rose, they were relieved by stopping therapy and giving alkali and fluids. No patient became comatose.

Hyperventilation This sign of toxicity began at a mean plasma-salicylate level of 32.8 mg per 100 c.c., the lowest individual instance being at a level of 21 mg per 100 c.c. and it tended to diminish if the concentration did not increase during the next few days. If the plasma level rose soon after hyperventilation started, dyspnoea became severe and therapy had to be interrupted. The gravity and frequent occurrence of this sign were considered sufficient to warrant a separate investigation, which is described below.

Pulmonary oedema One instance of acute pulmonary oedema occurred, which cleared rapidly with atropine, morphine, and oral sodium bicarbonate.

Haemorrhage Two cases of transient epistaxis were seen and one of fatal generalized haemorrhage. The fatality occurred in a woman of 41 years suffering from chronic rheumatoid arthritis, who received 10 gm of sodium salicylate in one litre of physiological saline intravenously daily for four days, followed by sodium salicylate and sodium bicarbonate 10 gm of each daily by mouth. A maximum plasma level of 59 mg per 100 c.c. was reached on the last day of parenteral therapy, accompanied by no major toxic symptoms. On the first day of oral therapy the plasma level was 55 mg per 100 c.c. On the second day when plasma levels were still falling hyperpnoea developed. Collapse occurred a few hours later with evidence of internal haemorrhage, and terminal haematuria. Prothrombin levels were not determined. Post-mortem examination revealed generalized haemorrhage of the serous and mucous surfaces with oedema cerebri and massive clots in the pleural cavities. Meyer and Howard (1943) were the first to show in man that coagulation time was increased and prothrombin diminished in the blood by administration of salicylate. In 1944 Stahmann, Huebner, and Link showed that salicylic acid is a 'degradation' product of the haemorrhagic agent hydroxycoumarin. In recent years case reports of death from haemorrhage in the course of salicylate therapy have been published by Ashworth and McKemie (1944) and Troll and Menten (1945). When the wide use of salicylate is considered, such cases must be regarded as rarities in the dosage commonly employed.

The toxic manifestations thus fall into three groups. In the first group are those that are relatively unimportant but common, tinnitus, headache, deafness, nausea, sweating, and transient vomiting, in the second are those that are uncommon though individually they may be serious, vertigo, drowsiness and mental upsets, pulmonary oedema, and haemorrhage, and in the third are those that are both common and alarming, hyperventilation and severe vomiting. During the treatment of patients suffering from rheumatic fever the first group of toxic symptoms was taken as an indication that the plasma concentration was approaching 35 mg per 100 c c, which Coburn (1943) considered an essential therapeutic level, and served as a guide to adequate dosage. Only on the appearance of the second and third groups of toxic symptoms was it necessary to modify or stop administration of sodium salicylate. It was our practice to maintain plasma concentrations between 30 and 35 mg per 100 c c for five to seven days, during which time the clinical features of rheumatic fever were well controlled. After this period the patients tolerated the higher plasma concentrations of salicylate with less severe and less frequent toxic manifestations. The dose required to produce and maintain a pre-determined plasma level depends on a variety of factors to be dealt with at length in another paper. These factors are the body-weight of the patient, fluid intake, the concurrent administration of sodium bicarbonate or other alkali, the pH of the urine and urinary excretion of salicylate, and the route of administration whether this be oral, rectal, or intravenous. Vomiting and hyperventilation were of most importance in the management of salicylate therapy and accordingly were the subject of further investigations.

The Emetic Action of Salicylate

Vomiting is one of the most disturbing features of salicylate intoxication and if persistent results in dehydration and may interrupt treatment. It occurs when salicylate is given by the oral, rectal, or intravenous routes. Samples of gastric content were aspirated from patients receiving salicylate by the rectal or intravenous routes. In no case was sodium salicylate detected in the samples obtained, which is in agreement with the findings of Caravati and Cosgrove (1946). In those patients who vomited during intravenous or rectal administration of salicylate, no drug was detected in the vomitus. In eight cases of emesis after salicylate therapy by mouth the plasma-salicylate level at the onset of vomiting was from 16 to 36 mg per 100 c c with a mean of 28.2 mg per 100 c c, whereas in seven cases of emesis during rectal or intravenous salicylate therapy the plasma level was from 30 to 40.5 mg per 100 c c, with a mean of 39.2 mg per 100 c c. There was no significant difference in the figures obtained from patients receiving salicylate by the intravenous route or *per rectum*. The lower plasma levels at which vomiting occurred when salicylate was given by mouth suggest that local gastric irritation is a factor in producing emesis, but the occurrence of vomiting after intravenous administration

of sodium salicylate in the absence of salicylate in the stomach contents indicates that the main cause is central rather than local

The Hyperpnoeic Action of Salicylate

As already stated, hyperventilation occurred frequently in patients and was associated with high plasma levels of salicylate (mean 32.8 mg per 100 c.c.) It was not seen when the plasma-salicylate figure was below 21 mg per 100 c.c. It was often alarming to the patient and interfered with treatment in that sodium bicarbonate had to be given or salicylate intake lowered in order to reduce the plasma-salicylate level. If the plasma level was permitted to rise within the next 24 hours, dyspnoea ensued and occasionally developed to an alarming degree. The underlying mechanism producing this hyperpnoea is difficult to explain. Johnson (1930), on the basis of examinations of the blood alkali reserve, interpreted the hyperventilation as being due to a fixed acid acidosis, as did Fashena and Walker (1944). Morris and Graham (1931) described the condition as a non-gaseous acidosis. Odin (1932) found respiratory alkalosis, and this interpretation has been supported by Rapoport, Wing, and Guest (1943), Ryder, Shaver, and Ferris (1945), and Erganian, Forbes, and Case (1947).

The mechanism of stimulation In an attempt to prove whether the hyperventilation was caused by acid-base change in the blood followed by alteration in the respiration, or whether it was caused by an intrinsic action of salicylate on the respiratory mechanism followed by blood changes consequent upon the hyperpnoea, the following investigations were made in animals and in man.

In rabbits anaesthetized with urethane, 0.04 gm per kg of sodium salicylate injected intravenously in 2 c.c. of saline produced immediate stimulation of respiration and irregularity of the blood-pressure, while three times this amount lowered the blood-pressure, depressed respiration, and produced clonic convulsions of considerable severity. Cats anaesthetized with ether, chloralose, or nembutal were not so sensitive. A dose of 0.1 gm of salicylate per kg injected in 30 sec in 2 c.c. of saline produced a transient rise in blood-pressure lasting one minute, and an increase in the rate and depth of breathing lasting 30 min. Immediately after injection the plasma-salicylate level rose sharply from zero to a maximum (mean of the maximum figures obtained in four cats was 88.8 mg per 100 c.c.). At this point in time, stimulation of respiration and rise of blood-pressure were marked, but the carbon dioxide combining power of the blood-plasma in a sample withdrawn some 45 sec after hyperventilation had begun was unchanged from its pre-injection level (mean figure obtained, 42.3 vol per 100 c.c.). In the course of the next six minutes the plasma-salicylate figure fell rapidly as a result of diffusion of salicylate into the tissue fluids (mean figure in the plasma after six min, 34 mg per 100 c.c.) and during this time the carbon dioxide combining power of the blood-plasma declined (mean figure at six min, 34.6 vol per 100 c.c.). After half an hour the salicylate level was still fairly high (mean figure, 25 mg per 100 c.c.), respiration was still increased, and carbon dioxide combining power reduced (mean figure, 32.6 vol. per 100 c.c.)

Fig 1 provides a graphic illustration of the time relations of these occurrences which shows that the stimulation of respiration coincides with the injection of salicylate and that the change in blood base relationships is apparently secondary to the hyperpnoea induced by salicylate. Further proof of

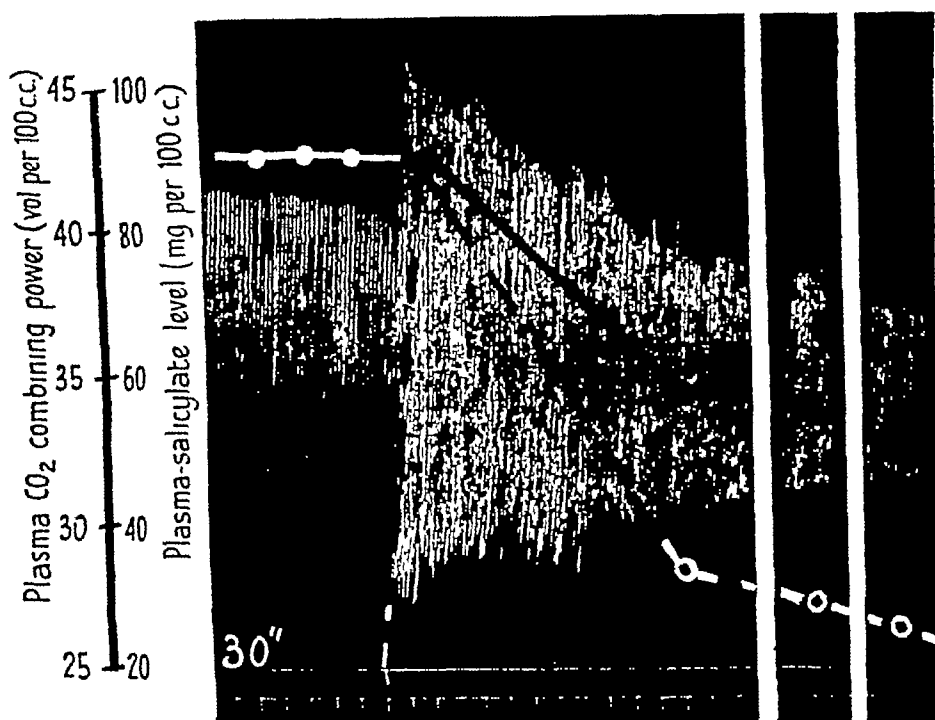


FIG 1 Cat ♂ 3.2 kg Chloralose 80 mg per kg. The top kymograph record shows respiration (inspiration downwards), middle line point of injection of salicylate, and lowest line time in 30 sec. Superimposed is a record of the plasma salicylate levels (interrupted line) and the blood plasma carbon dioxide combining power (solid line) after the injection of 0.1 gm per kg of sodium salicylate in 1.0 cc of saline. Note that hyperventilation follows immediately upon the injection of salicylate. A sample taken some 45 sec after the establishment of hyperventilation shows no fall in plasma carbon dioxide combining power. Increased respiration is not consequent upon fall in blood base.

this contention is provided by the finding that sodium salicylate in doses sufficient to stimulate respiration is equally effective in cats and rabbits whether given in distilled water or in 5 per cent solution of sodium bicarbonate (5 c c), with sodium lactate 0.2 gm per kg, or in 10 per cent calcium gluconate 2 c c. In this series of experiments it was also noted that previous administration of respiratory depressants such as morphine 1 mg per kg or hexobarbitone soluble 0.2 gm per kg caused no appreciable diminution in the stimulant action of the massive dose of salicylate administered.

Eight adult male patients suffering from chronic rheumatoid arthritis were chosen for experiment, the resting respiratory rate being recorded and the plasma carbon dioxide combining power determined on two consecutive days. Varying doses of sodium salicylate were then given intravenously on alternate

days for three days, during which time a daily estimation of plasma-salicylate level, carbon dioxide combining power, and respiratory rate was made. In the majority of cases the rate of breathing was not markedly increased, but the depth and force of respiration were obviously greater than before salicylate was given,

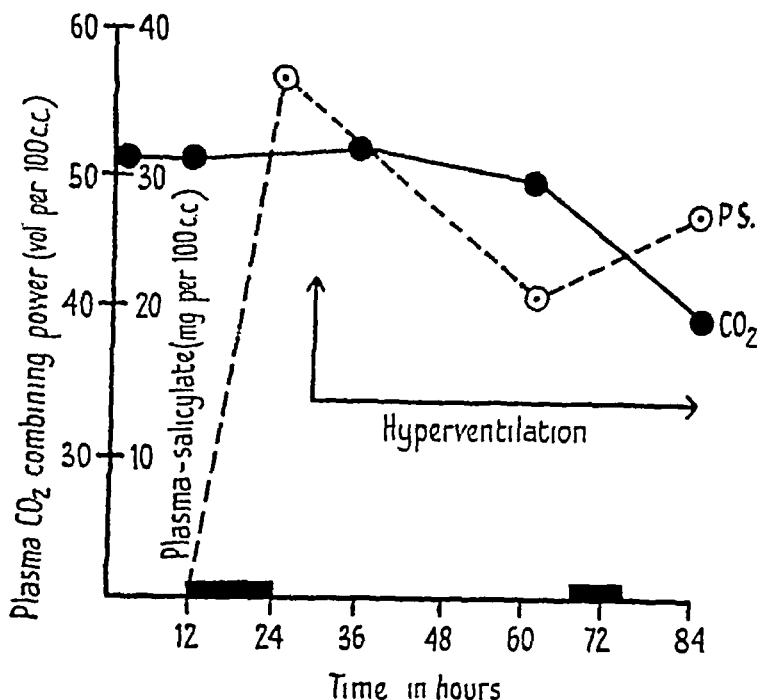


FIG 2 A record of the plasma carbon dioxide combining power in vol per 100 c c , and plasma salicylate level in a patient with rheumatoid arthritis. Intravenous sodium salicylate (one litre of 1 per cent solution) 10 gm given in 12 hours on first day, repeated in eight hours on third day. The depth of breathing increases with the advent of salicylate in the blood, but the fall in carbon dioxide combining power is delayed. Salicylate stimulates respiration directly, which is followed by a gaseous alkalosis.

so that the amount of tidal air respired must have been increased. The tidal air was not measured, but clinical notes were kept of the respiratory rate and the type of breathing present. The increase in respiratory effort was noted before the blood plasma carbon dioxide combining power began to fall. Fig 2 shows the record of a patient, wherein it is seen that increased respiration accompanied the rise in plasma-salicylate and preceded the fall in blood base.

These figures are interpreted as supporting the results already described in animals that salicylate causes a primary stimulation of the mechanism of respiration which is followed by a respiratory alkalosis. The stimulant action on respiration might be due to the effect of salicylic acid in altering blood pH, or to an intrinsic stimulant action of salicylate on the respiratory mechanism. The nature of the stimulation was not determined but intracellular dissociation of salicylate with alteration in pH is conceivable. The effect follows immediately

upon the injection of the solution, and Rapoport and Guest (1945) could find no alteration in blood pH after salicylate administration. Large doses of alkali do not inhibit the stimulant action, which cannot be due to the production of ketones (Myers and Ferguson, 1929), or to displacement of carbon dioxide by salicylic acid (Morris and Graham, 1931). It is therefore concluded that salicylate has a direct stimulant effect on the respiratory mechanism which is independent of alteration of the blood acid-base balance.

The site of stimulation. Drugs stimulating respiration may influence the activity of the respiratory centre directly, or through alterations in blood pH, or reflexly by various afferent nerve pathways. The last may be somatic or autonomic afferents, but the pathways from the carotid bodies, aortic arch, and lungs are all held to be of importance. It has been assumed (Goodman and Gilman, 1941) that the stimulant action of sodium salicylate on the respiration was a direct one on the respiratory centre, despite the forgotten observation of Danewski (1876) that vagotomy in experimental animals inhibited this effect.

Eight cats and six rabbits were anaesthetized and the blood-pressure and respiration recorded. It was found that the stimulant effect on respiration of a suitable dose of salicylate was not affected by extirpation of the carotid bodies, nor by previous administration of sufficient atropine sulphate to abolish the cardiovascular actions of vagal stimulation or injected acetylcholine. It was invariably found that bilateral vagotomy in the neck altered the rhythm of breathing, and that injected salicylate failed to stimulate this rhythm to any significant degree. This effect of vagotomy in inhibiting the stimulation of respiration by salicylate is shown in Fig 3. It is therefore concluded that the site of stimulation is a peripheral one acting through vagal afferent nerve fibres.

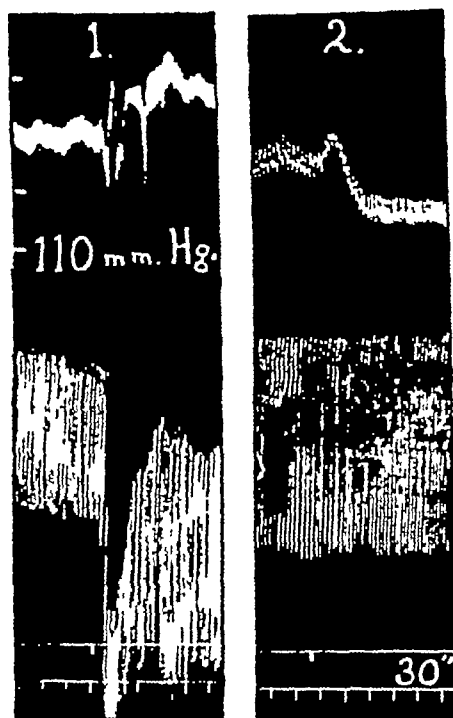


FIG 3. Cat ♂ 3.0 kg. Chloralose 80 mg per kg. The top record shows carotid blood-pressure, the next, respiration (inspiration downwards), then injection signal, and time in 30 sec intervals. At 1, injection of 0.1 gm per kg of sodium salicylate in 10 c.c. of saline causes irregularity in blood pressure and stimulation of respiration. Between 1 and 2, bilateral vagotomy and an interval of one hour. At 2, injection of the same dose of salicylate causes a fall in pressure, but no effect on respiration. Stimulation of the respiratory centre by salicylate is mediated by vagal afferent impulses. The fall in blood-pressure seen in 2 is partly masked in 1 by the effects of hyperpnoea.

Discussion

All our observations have suggested that the hyperventilation which occurs at high plasma-salicylate concentrations during sodium salicylate therapy is caused by stimulation of a peripheral receptor mechanism of a reflex arc, the afferent pathway of which is found in the vagus nerves. This hyperventilation when established produces a gaseous alkalosis which is followed by a reduced carbon dioxide combining power of the plasma. Smull, Wégria, and Leland (1944) and Smith, Gleason, Stoll, and Ogorzalek (1946) have shown that the administration of sodium bicarbonate to patients receiving sodium salicylate brings about a fall in plasma-salicylate levels. That this effect is produced by increased urinary excretion of salicylate was shown by Smith, Gleason, Stoll, and Ogorzalek (1946). It is suggested that continuous administration of sodium bicarbonate to patients abolishes hyperventilation because the sodium bicarbonate reduces plasma-salicylate below the critical level at which hyperpnoea develops. As was stated previously, this level was found to be between 21 and 44.2 mg per 100 c.c. The observed inability of large doses of alkali to prevent immediate and marked hyperventilation in animals after the intravenous injection of mixtures of sodium bicarbonate and sodium salicylate supports the contention that the hyperpnoeic action of salicylate results from an intrinsic effect of the salicylate on the respiratory mechanism, and not as a result of alteration of blood pH or change in plasma alkali reserve. The reduction in plasma alkali reserve after salicylate administration is consequent upon the hyperpnoea, as Figs 1 and 2 show. The clinical observation that concurrent administration of sodium bicarbonate with sodium salicylate tends to prevent reduction in the alkali reserve and hyperventilation may be explained thus: Concurrent administration of sodium bicarbonate lowers the plasma-salicylate level, reduces the stimulation of the reflex path in the afferent vagal branches, thereby reducing hyperventilation, and allowing the carbon dioxide combining power to return to normal.

Summary

1 The plasma level of salicylate was estimated in 70 patients receiving sodium salicylate in varying doses orally, rectally, or intravenously. This estimation was carried out on each occasion in the first week of therapy when toxic symptoms attributable to salicylate were noticed.

2 A total of 58 patients developed toxic symptoms of varying severity. These appeared in a definite order and were related primarily to plasma-salicylate levels, although tolerance to salicylate developed with continued therapy. The presence of tinnitus, deafness, nausea, and transient vomiting served as a guide for dosage and indicated that plasma concentration was approaching 35 mg per 100 c.c., above which level the toxic manifestations were more severe and often necessitated modification of therapy.

3 Of the more severe toxic effects, vomiting is largely of central origin, but a local irritant action in the stomach with oral dosage is probable.

4 Hyperventilation is due to reflex stimulation of the respiratory centre through the afferent fibres of the vagus nerve, and is independent of the blood acid-base relationship

5 Sodium bicarbonate administered by mouth lowers plasma-salicylate levels and thus reduces hyperpnoea. The reduced plasma carbon dioxide combining power consequent upon hyperventilation accordingly returns to normal

6 Internal haemorrhage from the serous surfaces, though a rare complication of salicylate therapy, may be fatal

We desire to acknowledge our indebtedness to the late Professor N. Morris for his encouragement and advice. The work was carried out by one of us (J.D.P.G.) during the tenure of an Imperial Chemical Industries Fellowship in Pharmacology. Working expenses were defrayed by a grant from the Medical Research Council.

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EXPERIMENTAL OBSERVATIONS ON CHRONIC AGRANULOCYTOSIS¹

By GEORGE HICKIE

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Introduction

THE study of agranulocytosis has largely been confined to clinical observation, examination of the cytology of the blood and bone-marrow, and experiments on drug sensitivity, together with attempts to induce the condition in laboratory animals by various means. A search of the extensive literature about agranulocytosis in the past 25 years has revealed only three references to investigation of the effect of the affected patient's serum on normal leucocytes, and none of these was very informative. An experiment was carried out by Roberts and Kracke (1930) in which normal blood and blood derived from a case of acute agranulocytosis were mixed. Total and differential white-cell counts were made at regular intervals and were found to remain unchanged. Since Roberts and Kracke worked with fixed preparations, alterations only in the number of neutrophils could be observed, and therefore their statement that the serum from their case had no toxic effect on normal neutrophils is not wholly valid. Rutledge, Hansen-Prüss, and Thayer (1930) designed an experiment with their case of cyclical agranulocytosis in which this difficulty was overcome. The motility of normal neutrophils in the patient's serum was observed and contrasted with that shown when a control serum was employed. One experiment only was carried out, and it was observed that the neutrophils lost their motility and became rounded in half the time of the control. It was also noted that 'some of the previously active leucocytes were dissolved'. The only other reference found was an unsubstantiated statement by Beck (1933) that sera may contain substances leucotoxic for neutrophils of normal subjects even of the same blood group.

When an opportunity arose to study a patient, who maintained normal health in spite of persistent severe leucopenia, it was decided to investigate the bactericidal power of his blood and also any effect his serum might have on neutrophils from normal persons, in the hope that the nature of his granulopenia might be explained.

Case Report

The patient, a man of 70 years of age complaining of cough and loss of weight, was originally admitted to Harefield Emergency Medical Service Hospital for

¹ Received November 25, 1947

shown to be more than 16 units per c c, while at the time of their healing it had fallen to less than 2 units per c c. Secondly, a blood estimation of the anti-streptolysin O, obtained immediately after a relatively severe attack of ulcerative pharyngitis due to a haemolytic streptococcus, was more than 1,000 units per c c, and when he was well some months later it had fallen to 500 units per c c.

Methods

The functions of the polymorph leucocyte most readily susceptible of measurement are motility, phagocytosis, and the part played in the bactericidal power of the blood. Motility was discarded, as no simple quantitative test could be devised. Phagocytosis was estimated, either by the normal incubation methods or Wright's centrifuge method, the results of which are comparable (Fleming, 1927). Bactericidal power was estimated in slide-cells, first described by Wright, Colebrook, and Storer in 1923, and later used in many observations by Fleming in testing the effect of antiseptics on neutrophils. The basis of the technique was fully described by Wright (1921) and is essentially as follows. Two glass slides, separated by strips of paper soaked with vaseline, are placed one above the other so that a narrow enclosed space is formed between them. Into this space, blood, or other media containing organisms, may be introduced and the whole may be incubated appropriately. The colonies of organisms which then grow may be enumerated or otherwise studied. As a rule, control blood was obtained from the same healthy subject who remained haematologically normal throughout. In addition the results were frequently checked with blood taken from other normal persons. The technique employed required that agglutination of red cells should not take place, so that, since the patient was Group B, blood from Group O or B donors only could be used for control purposes. 'Liquoid' to a final strength of 1:1,000 was used to estimate the implant of viable bacteria. This gave a control solution of blood devoid of bactericidal power. 'Liquoid' (sodium polyanethol sulphonate) is an anticoagulant which completely destroys the bactericidal power of whole blood (Haebler and Miles, 1938). Whenever 'blood' was reconstituted by mixing serum and washed cells, equal volumes of the two constituents were employed so that the serum:cells ratio remained constant in all experiments. If serum had to be kept for more than an hour or two, it was stored in sealed tubes in a refrigerator, and in this way loss of carbon dioxide was reduced to a minimum, so that the pH of the prepared media did not appreciably alter.

Observations

Patient's leucocytes Estimations of polymorphonuclear emigration, both in capillary tubes and on slides, proved to be of limited value on account of the small numbers of neutrophils present. In phagocytic experiments, the occasional neutrophil present appeared to show normal activity. In any estimation of phagocytosis a few bacteria may be seen inside monocytes, and the patient's blood was not exceptional in this respect. It was concluded, however, that the

investigation in September 1943 His blood condition was discovered on routine examination, and the following blood count is typical of those found during a three-year period of observation

Red cells	4,880,000 per c mm
Haemoglobin	96%
White cells	3,200 per c mm
Neutrophils	0.5%
Eosinophils	1%
Basophils	2.5%
Lymphocytes	76.5%
Monocytes	19.5%

His total white count did not vary much, ranging from 2,000 to 4,000 per c mm, with a mean of 2,400 per c mm. In 67 differential white counts, each of 500 cells, there were 26 occasions on which no neutrophil could be found, and a further 19 on which less than 1 per cent was found. An isolated finding of 360 per c mm was the highest recorded neutrophil count. The peripheral blood constantly showed a relative, and often an absolute, monocytosis. The sternal marrow was examined on three occasions and always showed marked myeloid hypoplasia, other elements being normal. These marrow counts were spread over a three-year period and the myeloid elements formed only 4, 12, and 7 per cent of all the marrow cells on these occasions. The following is one of these counts, supravital preparations confirmed the predominance of lymphoid cells

Total nucleated cell count	10,000 per c mm
Myeloblasts	0%
Promyelocytes	0%
Neutrophil myelocytes	1%
Eosinophil myelocytes	1%
Neutrophil metamyelocytes	1.5%
Neutrophil granulocytes	3.5%
Proerythroblasts	0.5%
Megaloblasts	7.5%
Basophil normoblasts	1%
Polychromatic normoblasts	7.5%
Orthochromatic normoblasts	32.5%
Lymphocytes	42%
Monocytes	1%
Unidentified cells	1%

His past history and family history did not contain anything relevant to his present condition. In the three years during which he was under observation he remained for the most part in good health, despite the state of his blood. His liability to infection did not seem to be much greater than normal, but he had during this time a small number of superficial staphylococcal and haemolytic streptococcal infections. These showed no tendency to spread and always healed with local treatment, chemotherapy not being used. During these acute infections there was no change in the differential white count. Unfortunately histological evidence of the nature of the cellular exudate in these inflammatory lesions was not obtained, but swabs taken from the surface showed mainly necrotic debris and no polymorphs were seen. In relation to these infections, two further facts of interest are recorded. Firstly, just prior to an outbreak of boils, the staphylococcal antitoxin in the patient's blood was estimated and

It is seen that the patient's serum acting on normal cells completely destroyed their bactericidal power, the result was the same when cells from other normal persons were used. The discrepancy between the almost normal opsonic index

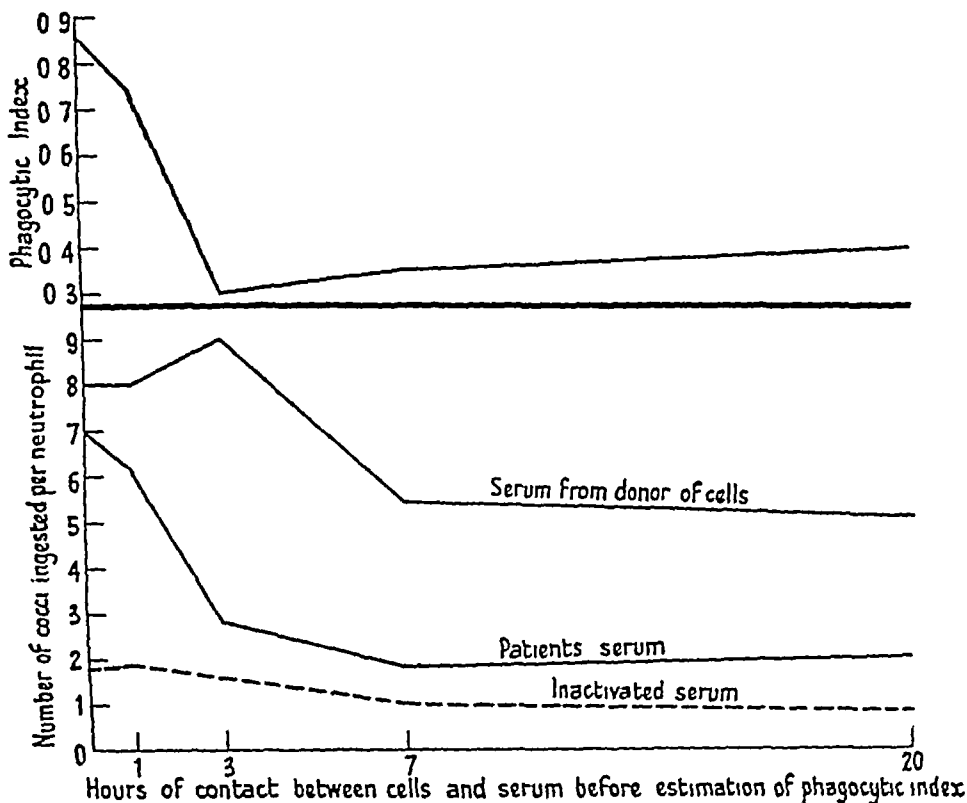


FIG 1

and the absent bactericidal power may be explained by the difference in the time factor and the number of bacteria employed. In the opsonic estimation there is a short exposure to many cocci, while in the test for bactericidal power there is a long exposure to a small number of cocci.

Toxicity of the patient's serum It seemed probable that the effect shown in Table II might be due either to a toxic action by the patient's serum or to a deficiency in that serum of some factor essential to the bactericidal power of whole blood. To investigate this point serum from the patient and from the control were mixed in the proportions shown in Table III, and an equal volume of washed normal cells was added to each mixture. The addition of staphylococcus suspension and incubation in slide-cells were carried out as before. Enumeration of the colonies again showed failure of the bactericidal power of normal leucocytes in the presence of the patient's serum, but the effect of varying the proportions of the two sera was surprising. This antagonism is shown only when the patient's serum is present in high concentration and high dilution, whereas when the two sera are present in equal amounts the bactericidal power

greater part of the phagocytic power of the patient's blood had been lost, because the neutrophils were so few -

The bactericidal power of the patient's blood was compared with that of a normal person (the author) in the following way. Dilutions were made of a 12-hour broth culture of staphylococcus, 5 c mm of the bacterial suspension were added to 50 c mm of defibrinated blood, and, after mixing, incubation carried out in slide-cells. On the following day the colonies which had developed were counted. A control was made by the addition of 'Liquoid' to normal blood, and the colonies which developed were regarded as an estimate of the viable bacteria implanted. The results, shown in Table I, are from one of several experiments, all of which demonstrated that the patient's blood had no bactericidal power against the staphylococcus *in vitro*. In view of conclusions drawn from later experiments, the observed correlation between absence of neutrophils and absence of bactericidal power is important and is therefore emphasized.

TABLE I

Blood	Dilution of Staphylococcus culture			
	1/4,000	1/16,000	1/32,000	1/128,000
	Colonies developing in slide-cell			
Patient	110	39	26	5
Normal	6			
'Liquoid' control	137	33	27	5

Action of the patient's serum on normal cells. Blood was withdrawn from the patient and from the normal control. Both samples were defibrinated and centrifuged, after which the serum was removed. The cells from the normal blood were then washed in three changes of isotonic saline.

The opsonic index of the patient's serum was first determined. To one volume of washed cells and one volume of serum were added two volumes of staphylococcus suspension. The mixtures were incubated for 15 min and the cocci taken up by 50 polymorphs counted, with the normal serum, 50 cells ingested 166 cocci, and with the patient's serum, 148 cocci. The opsonic index of the patient's serum was therefore 0.82.

Equal volumes of serum and washed cells from patient and control were made up as shown in Table II, the staphylococcus suspension was added, and the infected blood incubated overnight in slide-cells. Next day the colonies, which had developed, were enumerated. The control was made by the addition of 'Liquoid' to a mixture of normal cells and normal serum.

TABLE II

Cells	Serum	Dilution of Staphylococcus culture			
		1/8,000	1/16,000	1/32,000	1/64,000
		Number of colonies developing in slide-cell			
Patient	Patient	x	120	63	27
Normal	Normal	1			
Normal	Patient	x	97	38	28
Patient	Normal	x	112	41	23
'Liquoid' control		x	108	60	23

Where x indicates a number too great to count

The possible significance of this unusual finding is discussed and elaborated below

Time factor in toxicity Normal washed cells were suspended in normal serum and also in the patient's serum, these mixtures were then separately placed in an incubator and samples withdrawn at intervals. Total and differential white-cell counts were made on the mixtures before and after the experiment, and there was a slight but definite fall in the total and alteration in the differential white-cell counts. These changes were not due to a specific effect of the patient's serum, as they were closely similar in both mixtures. Thus, in the patient's serum the total white count fell from 4,200 to 3,800 per c mm, and in the normal serum from 4,000 to 3,700 per c mm. The neutrophil count in the experiment with the patient's serum fell from 74 to 53 per cent, and with the normal serum from 75 to 58 per cent. Phagocytosis of a suspension of staphylococci in the mixtures was then estimated by Wright's centrifuge method, 50 cells being counted for each estimation. The results appear in Table V and Fig 1

TABLE V

	<i>Time in hours of taking samples</i>				
	0	1	3	7	20
Cocci ingested in normal serum	406	406	449	279	256
Cocci ingested in patient's serum	344	311	138	96	103
Phagocytic index of patient's serum	0.84	0.76	0.30	0.34	0.40

While the initial phagocytic index was slightly under normal (almost the same as on the previous determination) it fell rapidly as the time of contact between the normal cells and the patient's serum was increased. Thus, in the presence of the patient's serum the phagocytic power of the cells fell to 30 per cent in three hours, while it was still above this figure after 20 hours in normal serum. A control was made with serum inactivated at 56° C, which gave a uniformly low level of phagocytosis which did not alter during the period of the experiment. It was not made clear by these experiments whether the action of the patient's serum was lethal to the neutrophils, or whether it was merely inhibitory. A further experiment was therefore carried out, in which normal cells were again subjected to the action of the patient's serum for varying periods. Normal defibrinated blood was divided into three equal volumes, of which one was at once put into an incubator. The other two were centrifuged, the serum pipetted off, and the cell-residue washed in three changes of isotonic saline. These two fractions of normal blood cells were now resuspended respectively in equal volumes of normal and patient's serum. The mixtures were then incubated at 37° C with the untreated blood. At intervals samples were withdrawn from each of the three tubes. Samples from the first were mixed with staphylococcus suspension and incubated in slide-cells. Samples from the other two were removed, 15 volumes of saline added, and centrifuged. This method of washing was adopted in order to reduce to a minimum the trauma of centrifugalization. To the two cell residues were added equal volumes of normal fresh serum, after the supernatant saline had been poured off. The staphylococcus suspension was added and incubation carried out in slide-cells as before. In this experiment,

is almost normal. It will be seen that the patient's serum does not behave as does an 'inert' serum (that is, serum inactivated at 56° C, the effect of which is shown in Fig 2), for in such circumstances the bactericidal power is maintained

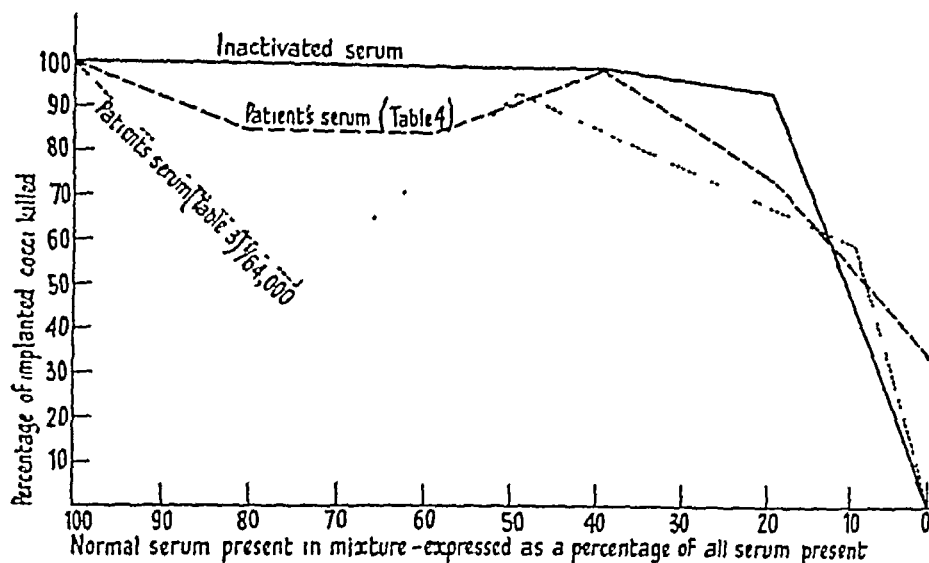


FIG 2

until a critical level of normal serum is reached, this level being usually less than 20 per cent of normal serum. Nor did it appear to have a simple inhibitory effect on leucocytes, for had this been so the resulting graph would have been of the same shape as that for an inert serum, but with the critical level shifted to the left. Since the observed result did not conform with either of these

TABLE III

Serum as percentage of total		Dilution of staphylococcus culture			
Patient	Normal	1/8,000	1/16,000	1/32,000	1/64,000
		Number of colonies developing in slide-cell			
	100	9	1	1	
25	75	75	35	11	9
50	50	6	4	1	1
90	10	26	18	9	8
100		56	43	26	18

expectations and gave a curve of unlikely shape, the experiment was repeated using more numerous dilutions of serum and only one suspension of staphylococcus. The technique used was essentially similar to that described above. Ten such confirmatory experiments were carried out and, as the implant was the same and all the results comparable, the aggregate of all the colonies developing for each dilution is shown in Table IV and Fig 2.

TABLE IV

Cocci implanted in each cell	500	500	500	500	500	500
Patient's serum, percentage		20	40	60	80	100
Normal serum, percentage	100	80	60	40	20	
Colonies developing from 500 cocci	6	75	17	2	135	322

and also the time of contact, are borne in mind, the unexpected results of this investigation, which otherwise may appear paradoxical, may be explained. At first sight it appears contradictory that the phagocytic index of the patient's serum is normal while its bactericidal power is almost nil. However, as was seen in the experiment shown in Table V, when the period of action of the patient's serum on normal cells was increased before the bacterial suspension was added, the phagocytic power fell sharply. By this technique one of the major differences between the phagocytic and bactericidal experiments is eliminated, and the results immediately become more closely comparable.

Theoretically, it seems possible that the remarkable effect of the patient's serum on normal cells might be due either to the presence of some substance or substances inhibitory to the functions of the neutrophils, or to the absence from the serum of substances which are essential for their proper functioning. Two conclusions may be drawn from these experiments, which together suggest that the effect is due to an inhibitory substance or substances. Firstly, there is the fact that the phagocytic power of the cells is normal if estimated at once, but falls sharply if the serum and cells are in contact for some time before the test is made. Secondly, there is evidence (shown in Table IV and Fig. 2) that dilution of normal serum with inactivated serum does not affect the bactericidal power until a critical level is reached with less than 20 per cent. of normal serum in the mixture. On the other hand, when the patient's serum is used as the diluent of normal serum there is a marked fall in the bactericidal power when there is still 80 per cent. of normal serum present. The explanation of this result is not clear, for it is found that the bactericidal power recovers as the proportion of the patient's serum is increased, only to fall away again as the amount of patient's serum approaches 100 per cent. concentration. No entirely satisfactory explanation can be found for this phenomenon, and, at the moment, it is only possible to indicate its constancy.

Summary

- 1 A man, aged 70 years, has been under observation for three years in a condition of unremitting agranulocytosis while his health has been, on the whole, good.
- 2 The patient's blood lacked the bactericidal power against the staphylococcus *in vitro* which is found in all normal bloods.
- 3 The patient's serum was antagonistic to normal neutrophil activity. The action was not instantaneous, nor was it lethal to leucocytes even after prolonged periods.
- 4 The nature of this antagonistic effect has not been fully established.
- 5 Figures are given which show that the patient had unusual powers of antibody production in relation to staphylococci and streptococci.

I wish to express my thanks to Sir Alexander Fleming for his advice throughout this investigation, to Dr E. W. Todd and Dr Leslie Hewitt for the

because of the time involved, more than one staphylococcal suspension had to be used. The number of cocci was carefully standardized and determined by the 'poured plate technique', but because it was not absolutely constant the results shown in Table VI are given as percentages of the implant killed instead of a direct count of the surviving bacteria as elsewhere in this paper. After 23 hours (that is, at the end of the experiment), to show the effect of the two sera with which the cells had been in contact, samples from the two tubes which contained reconstituted blood were mixed with staphylococci and incubated. The results, shown in Table VI, demonstrate that, even after so long an exposure to the action of the patient's serum, the neutrophils were not dead and could recover their activity in the presence of normal serum.

TABLE VI

<i>Time of sampling in hours</i>	<i>Percentage of implant killed</i>		
	<i>Normal blood</i>	<i>Patient's serum Normal cells</i>	<i>Normal serum Normal cells</i>
2 hr Fresh serum added after washing	99	93	95
5 hr Fresh serum added after washing	95	96	100
23 hr Fresh serum added after washing	78	42	65
23 hr No fresh serum, no washing of cells	78	6	67

Discussion

Fleming (1926) working with slide-cells, showed that the bactericidal power of whole blood against the staphylococcus, which was previously known to depend on the neutrophils, varied in direct proportion to the number of these cells present. If blood was diluted so that there were fewer neutrophils present in the slide-cell, the bactericidal power fell, the fall being greater if the diluent was a suspension of red cells than if it was normal saline. It seemed probable that the density of the medium was affecting the ability of the neutrophils to move about and ingest the cocci. His experiments further demonstrated that the antibacterial action of blood against the staphylococcus depends on the neutrophils and also that the slide-cell technique gave an indication of neutrophil motility, phagocytic power, and ability to destroy cocci which had been engulfed.

In the experiments described here the bactericidal power has been used as an index of neutrophil activity only, and no conclusions have been drawn as to its possible immunological significance. When the bactericidal power is estimated with the slide-cell there are present 50 c.mm. of normal blood, which contains approximately 100,000 neutrophils, there are also about 100 cocci, and the period of action of the test is measured in hours. In the technique described above for the estimation of the phagocytic power 50 c.mm. of blood are again present, but the cocci are numbered in millions and the period of action is measured in minutes. If the differences in the numbers of cocci and leucocytes,

THE KIDNEY IN PERIARTERITIS NODOSA¹

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With Plates 15 to 17

THE association of renal lesions with periarteritis nodosa has been known since the publication of the first comprehensive description of the disease by Kussmaul and Maier (1866). The frequency of renal involvement has been stated to be 73 per cent of cases (Gruber, 1925), 80 per cent of cases (Arkin, 1930), and 87 per cent of cases (Harris, Lynch, and O'Hare, 1939). Gruber's review of 108 cases from the literature shows that while multiple renal infarcts were a common finding, there were also cases in which diffuse changes in the renal parenchyma were present, and these were usually described as one or other form of nephritis. In the literature before and since Gruber's paper, opinions have varied as to the relation of these parenchymal changes to the periarteritis nodosa. Thus, Ophüls (1923) believed that the diffuse nephritis seen in periarteritis nodosa was an unrelated coincidental lesion, yet Kroetz (1921) thought that the same factor that involved the renal arteries was also the cause of the nephritic lesions. Meyer (1921) could not decide whether the nephritic lesions were secondary to the vascular involvement or directly due to a hypothetical toxic factor. Gray (1929) argued that the nephritic lesions were secondary to involvement of arterioles by periarteritis nodosa. Grant (1940) held that the renal changes were primary manifestations of periarteritis nodosa and not those of an independent glomerulonephritis. Furthermore, Löhlein (1907), Fishberg (1927), Russell (1929), and Koch (1931) have described arteritic lesions in the more rapidly progressive form of glomerulonephritis, and a number of authors (Schurmann and MacMahon, 1933, Friedberg and Gross, 1934, Mallory, 1936, Grant, 1939, Canny, 1940, Fahr, 1941, Moschowitz, 1945) have noted the similarity of the renal lesions in periarteritis nodosa to those seen in malignant nephrosclerosis.

The purpose of presenting the clinical and pathological features of the following cases is therefore, firstly, to describe the various renal lesions encountered, secondly, to attempt to establish histological criteria by which the renal lesions of periarteritis nodosa can be separated from those of nephritis or malignant nephrosclerosis, and, thirdly, to relate these findings with the clinical course of the disease, with a view to evaluating the possible aetiological role of those lesions in the production of hypertension and uraemia. Before describing our own cases in detail it will be of value to review briefly the clinical and pathological findings that have been described in periarteritis nodosa.

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antistreptolysin estimations, to the patient for his generous co operation, to Dr E I Jones, under whose care the patient was admitted to hospital, and to Dr W D W Brooks for his assistance in the presentation of this paper

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Histological Findings

Although the earlier reported cases of periarteritis nodosa showed naked-eye evidence of arterial involvement, it has since become recognized that the form of the disease in which the diagnosis can be made only after histological examination is the commoner (Klemperer, 1932, Spiegel, 1936, Sandler, 1938). The importance of a thorough histological examination has been repeatedly stressed (Gray, 1929) Spiegel (1936) and Grant (1939) laid special emphasis on the examination of serial sections, and Rothstem and Welt (1933) on the importance of examining numerous organs. The essential lesion in the acute stage consists of fibrinoid necrosis of part or all of an artery wall together with a perivascular cellular infiltration consisting of varying proportions of neutrophils, eosinophils, and lymphocytes. Typically the lesion is segmental, involving but one portion of the circumference of a vessel. Usually arteries of medium size are involved, but arterioles and even capillaries may be attacked (Kussmaul and Maier, 1866, Macaigne and Nicaud, 1932, Spiegel, 1936). The damage to the arterial wall may lead to aneurysm formation and thrombus. Next, intimal proliferation develops, and extends both above and below the site of the initial necrotic lesion. Fibrous proliferation of the adventitia and fibrous replacement of the damaged part of the media take place. If thrombosis has occurred, organization and in some cases recanalization of the thrombus ensues. An elastic stain often shows rupture or partial loss of the internal elastic lamella (Meyer, 1921, Wohlwill, 1923, Gohrbandt, 1927, Hinrichs, 1931). Later still the inflammatory cells have disappeared, and an artery in the healed phase sectioned above or below the site of the initial necrotic lesions may show merely intimal hyperplasia, the media and internal elastic lamella appearing intact, but a study of serial sections, some of which pass through the original necrotic lesion, will show medial fibrosis, and fracture or partial loss of the internal elastic lamella. Lesions similar to the acute lesions of periarteritis nodosa may be found in scleroderma, acute disseminate lupus, and in Libman-Sach's syndrome (Pollack, 1940, Klemperer, Pollack, and Baehr, 1941). In order to limit the field of our inquiry we have excluded any case from the present series in which any of these conditions might have been diagnosed on clinical or other grounds.

Material and Methods

The material of the study consists of 14 cases, which came to autopsy between 1934 and 1947. In the three cases with aneurysm formation the diagnosis of periarteritis nodosa was made at autopsy or before, and numerous organs were sectioned histologically, but in most of the remainder the correct diagnosis was not made macroscopically, and the number of organs of which histological preparations were available was limited. In every case all available tissue was sectioned by the paraffin method and stained by haemalum and eosin, and by Weigert's elastic stain and van Gieson's stain combination. Gram's stain, Ziehl-Neelsen's stain, Weigert's fibrin stain, and methyl violet for amyloid degeneration were also used when required. At least 100 consecutive sections

Clinical Features

Several excellent reviews of this aspect of the subject have recently been published, as, for instance, those by Leishman (1937), Harris, Lynch, and O'Hare (1939), and Grant (1939), and we do not therefore propose to give a full account of the clinical findings. Those who have read the literature may gain the impression that the symptoms of periarthritis nodosa are so varied that almost any syndrome, if somewhat bizarre and unfamiliar, can be encountered in this disease. In actual experience this is not so. Though the disease may appear in many forms, there is a certain recognizable clinical pattern which suggests the diagnosis in the majority of cases. Typically the illness is protracted and pyrexial. The pulse is rapid, weakness is an early complaint, limb pains, often diagnosed as rheumatism, are early and frequent, and later they may take on a neuritic form. At some time during the illness visceral disturbances occur, taking the form of asthma, atypical bronchopneumonia, or cardiac pain. Very frequently there is abdominal pain, sometimes with symptoms of perforation, peritonitis, or mesenteric thrombosis. Subcutaneous nodules may appear, but are not found in the majority of cases. Albuminuria, which is frequent, is often the only sign that the kidney is involved, but there may be haematuria, and the illness may terminate in renal failure. Hypertension occurs often and may dominate the clinical picture. Investigation shows a leucocytosis almost constantly, a high erythrocyte sedimentation rate, and a persistently negative blood culture. Eosinophilia may suggest the diagnosis, but occurs in less than 20 per cent of cases (Harris, Lynch, and O'Hare, 1939). It is known that recovery may occur, and also relapse. Permanent and severe hypertension may be a serious sequel when the disease is no longer active.

Autopsy Findings

The occurrence of visible nodular aneurysms along the course of the visceral arteries was the original basis for the recognition of periarthritis nodosa at autopsy. Much of the early literature was confined to descriptions of this type. The heart, kidneys, spleen, liver, intestine, lungs, and mesentery are commonly involved, the aneurysms are seen as greyish-yellow foci along the course of an artery, and on section they contain red thrombus. In such cases infarcts of the kidney may be numerous (Lamb, 1914, Kroetz, 1921, Otani, 1924, Vance and Graham, 1931). Infarcts in other organs are not uncommon, and according to Pass (1935) the most frequent cause of liver infarcts is periarthritis nodosa. In the lungs infarcts may occur, and also numerous greyish-white small foci resembling tubercles may be present. In cases where renal involvement without infarction has occurred, the kidneys have shown various appearances. The surface may be smooth or slightly uneven (Gruber, 1925) or definitely granular (Gohrbandt, 1927, Kimmelstiel, 1927, Hauser, 1928). On section the cortex may be mottled red and grey, or red and yellow (Singer, 1927, Nauheim, 1928). In the absence of aneurysms there are no naked-eye features in the kidneys that are peculiar to periarthritis nodosa.

Spleen Both splenic artery and vein contained ante-mortem thrombus, the appearance of the spleen suggested massive infarction

Kidneys (200 gm each) The capsules stripped easily, exposing a smooth surface, cortical striations were obscured, cortex and medulla were pale

The remaining organs showed no significant abnormality

Histological findings *Kidney vessels* Occasional interlobar and arcuate arteries showed typically segmented acute lesions of periarteritis nodosa (Plate 15, Fig 1) Intralobular arteries and afferent arterioles were normal

Glomeruli The normal number was present, but almost all were affected Over half showed patchy fibrinoid necrosis of the tufts (Plate 15, Figs 2 and 3) Epithelial crescent formation was widespread, often associated with the fibrinoid necrotic lesions (Plate 15, Fig 2) Some of the necrotic foci had associated polymorphonuclear cells Other tufts showed a few polymorphonuclears and endothelial cell proliferation Others showed various stages of fibroblastic organization of crescents, but no glomeruli had become completely fibrotic

Tubules These showed fairly uniform dilatation and were lined by atrophic flattened epithelium (Plate 15, Fig 2)

Interstitial tissue This was oedematous and early intertubular fibrosis was present Focal collections of polymorphonuclears, eosinophils, and lymphocytes were sparsely scattered throughout, and often had a periglomerular location.

Pelvis Appeared healthy

Spleen, lungs, and voluntary muscle from thigh showed typical lesions of periarteritis nodosa in the acute phase

Liver and heart No lesions were found

Summary This was an illness which lasted for a few months and was associated with pain in the arms, legs, chest, and abdomen There was sweating, weakness, and loss of weight, though we have no temperature record until the last few days Inflammation of the eyes was a troublesome complication which at one time dominated the clinical picture The blood-pressure was normal, there was a high leucocytosis The clinical picture is thus compatible with periarteritis nodosa, and although the illness terminated in uraemia it was at no time suggestive of any classical form of nephritis Histologically the diagnosis of periarteritis nodosa is based on the presence of necrotizing arteritis in the lung, muscle, and spleen, as well as in the kidney The renal parenchymal lesions present a distinctive histological picture dominated by focal necrotizing glomerulitis and epithelial crescent formation, which may be correlated with the uraemic termination

Case 2 History A man of 55 years was admitted on March 22, 1947, complaining of shortness of breath and pain in the chest Five weeks previously he had begun to feel ill and tired, and was seen by his doctor, who advised rest in bed After a few days he felt better and got up again Five days before admission the tiredness increased and a tight feeling in the chest developed He was put to bed and given a course of a sulphonamide totalling 6 gm Four days prior to admission dyspnoea commenced, and pain in the right side of the chest posteriorly on breathing During the period before admission the doctor had noticed an occasional rise in temperature to 101° F, the passing of dark urine, sweating, loss of weight, and on one occasion black stools The family history and previous medical history were not relevant

On examination the patient was dyspnoeic The temperature was 99.8° F, and pulse 96 to 120 There was bronchial breathing over the upper lobe of the right lung posteriorly with increased vocal resonance No adventitious sounds

from each block were obtained, and every 24th and 25th slide stained by haemalum and eosin and the elastic van Gieson combination, respectively, if necessary every 10th and 11th slides were also examined. A number of the cases were discovered in the course of a general survey of nephritis material still in progress, based on case notes and autopsy material that had accumulated during an 11-year period. The clinical aspects have necessarily been studied in retrospect from the case notes, and data have been lacking that might have been available if the patients had been seen by us during life.

Case Reports, Group A

The 14 cases have been divided into two main groups (A and B) based on the histological findings in the kidneys. In Group A severe and widespread glomerular damage was present, whereas in Group B glomerular changes were not widespread.

Case 1 History A man aged 41 years was transferred from the Royal Eye Hospital on January 4 and died on January 8, 1947. He complained of pain in the limbs, chest, and abdomen which he had had for 13 weeks. Eight months before, his right eye had become sore and begun to discharge. These features persisted, but the sight was unaffected. For the last week or two the left eye had also been sore. Five months before he had had a dental root extracted. Four months before he had had a Caldwell-Luc operation for chronic nasal discharge. For 3½ months he had had pain in the left calf muscles, which later spread to the ankles, arms, legs, chest, and abdomen. This persisted and was associated with sweating, weakness, and loss of weight. The pain in the chest was accentuated by deep breathing. There was no dysuria or haematuria.

On examination he appeared seriously ill. There was dyspnoea, pallor, and wasting. The pulse-rate was 88, there was an apical systolic murmur, and the blood-pressure was 140/90. There were signs of a left pleural effusion or collapse of the left lower lobe. The chest wall was tender on palpation, and the abdominal wall the same. The ankles were slightly swollen. The right eye was red, with inflamed sclera and conjunctiva. There was slight conjunctivitis on the left side. The blood-pressure on 2.1.47 was 140/80. Tests done at the Royal Eye Hospital on 3.1.47 gave the following results: Blood-sedimentation rate 24 mm in one hour, red cells 4,370,000 per c mm, haemoglobin 70 per cent, colour index 0.8, white cells 20,500 per c mm, differential count, polymorphonuclears 72.3 per cent, eosinophils 3.8 per cent, mononuclears 9.0 per cent, basophils 0.2 per cent, lymphocytes 14.7 per cent. At the Royal Infirmary the following investigations were made on 4.1.47. Urine, albumin 1 gm per litre, numerous white cells, red cells, and granular casts were present. The blood-urea was 458 mg per 100 c c. There was no pyrexia while he was in hospital. The charts show that sulphadiazine and penicillin were given from 4.1.47 to 6.1.47. He died suddenly on 8.1.47.

Summary of autopsy findings There were multiple thromboses in the superficial veins of upper limbs.

Heart (300 gm) Fibrinous pericarditis was present, but no endocarditis.

Left lung The smaller vessels contained ante-mortem thrombus, scattered small infarcts were present.

Right lung There was congestion and oedema only.

were heard. No abnormality was noted in the cardiovascular or nervous systems. The blood-pressure was 120/70. A blood count showed red cells 4,880,000 per c mm, haemoglobin 96 per cent, white cells 18,000 per c mm, differential count, polymorphonuclears 83.5 per cent, lymphocytes 10.5 per cent, monocytes 4.5 per cent, eosinophils 1.5 per cent. The urine contained albumin throughout the illness. The blood-urea was not recorded. X-rays of the chest (24.3.47) showed patchy consolidation of the right upper lobe. A blood culture (27.3.47) was sterile. The sputum (31.3.47) showed no tubercle bacilli. The leucocyte count rose to 24,000 per c.mm. The patient was thought to have an unresolved pneumonia and a course of sulphamethazine was started. Thirty-six hours' treatment had no effect on the temperature, which was swinging between 98° and 102° F. Penicillin therapy (30,000 units three hourly) was then instituted. After 48 hours the temperature showed no response. The patient was more exhausted, the dyspnoea and cyanosis increased, and the pulse-rate remained at about 100. The temperature continued to vary between 98° and 102° F until April 3 when the patient died.

Summary of autopsy findings. *Heart* (450 gm.) The left ventricle was enlarged, no evidence of endocarditis was found.

Right lung. The apical region showed greyish-white patchy consolidation.

Spleen (600 gm.) Cut surface firm, no visible abnormality.

Right kidney (290 gm.) Cortex thickened, pattern somewhat obscured.

Left kidney (250 gm.) Similar to right.

The remaining organs showed no significant abnormality.

Histological findings. *Kidney vessels.* Some of the arcuate and a few of the intralobular arteries showed lesions of the acute phase of periarteritis nodosa, the afferent arterioles were normal.

Glomeruli. The normal number was present, more than half showed patchy fibrinoid necrosis of the tufts (Plate 15, Fig. 4) in every way similar to the glomerular lesions in Case 1. All showed varying degrees of endothelial cell hyperplasia, and infiltration of the tufts by polymorphonuclears. Occasional epithelial crescents were present. No fibrotic glomeruli were seen.

Tubules. These were not dilated, many cells showed hyaline droplet degeneration.

Interstitial tissue. Focal collections of polymorphonuclears, lymphocytes, and plasma cells were scattered in the cortex, often with a periglomerular location.

Pelvis. Healthy.

Kidney, spleen, and lung were available for histological examination, typical acute lesions of periarteritis nodosa were present in all three organs.

Summary. This short general illness with pulmonary signs, pyrexia, and leucocytosis could have been ascribed to an atypical unresolved pneumonia, and this was the clinical diagnosis made. There was, however, no response to sulphonamides or penicillin, and there was albuminuria throughout the illness. This, and the passing of a black stool on one occasion (which was confirmed by his doctor) show that the illness was not localized to the chest. The clinical history is therefore compatible with periarteritis nodosa. The blood-pressure was normal, but unfortunately the blood-urea was never estimated. Pathologically this was an example of the microscopic form of periarteritis nodosa in which necrotizing arteritis was present in kidneys, spleen, and lung. The kidneys showed diffuse acute glomerulitis with focal fibrinoid necrosis in over half the tufts, the glomerular lesions being substantially similar to those of Case 1, but polymorphonuclear infiltration was more prominent.

Case 3 History. A male clerk aged 55 years, was admitted to another

organization. Occasional glomeruli were completely fibrotic. Only occasional polymorphonuclears were present in the necrotic tufts.

The tubules were not dilated, the epithelium showed post-mortem changes.

Interstitial tissue. There was no definite increase in fibrous tissue, many periglomerular collections of lymphocytes were present.

The spleen presented throughout many ill-defined areas of necrosis infiltrated with polymorphonuclears, some of the necrotic areas showed varying degrees of fibroblastic organization. Many of the central arterioles of the Malpighian bodies appeared to have been destroyed by necrotizing arteritis (Plate 16, Fig 8) and the bodies themselves were in the main unrecognizable. The larger splenic arteries were unaffected. The necrotic areas were negative for bacteria, including tubercle bacilli.

Lung. Only tissue from the apices was available and sections showed areas of recent haemorrhage, fibrinoid necrosis occurring in fibrous tissue, and areas of fibroblastic organization. One or two large vessels showed lesions typical of the acute phase of periarteritis nodosa. There was no evidence of tuberculosis histologically. Stains for tubercle bacilli and other bacteria were negative.

Thyroid. No lesions of periarteritis nodosa were seen.

Summary. Progress notes were scanty in this case and it is impossible in retrospect to gain an adequate impression of the illness. There was pyrexia and leucocytosis with chest signs and albuminuria. Pathologically this was a case of periarteritis nodosa in which the lesions in the lung and spleen appeared to the naked eye to be tubercles, but on section the histological features of tuberculosis were not present, the lesions were abacterial and associated in both organs with necrotizing arteritis typical of the acute phase of periarteritis nodosa. No arteritic lesions were present in the renal vessels, but the diffuse parenchymal changes were essentially similar to those of the preceding cases. That this was a case of periarteritis nodosa was first suspected after histological examination of the kidney had revealed the essential similarity of the parenchymal lesions with those of known cases of periarteritis nodosa (Cases 1, 2, and 3). Subsequent critical examination of slides of the lung and spleen then provided confirmatory evidence of the diagnosis.

Case 5. No clinical records were available for this patient, who was a woman aged 53 years, who came to autopsy with a clinical diagnosis of bronchopneumonia.

Summary of autopsy findings. *Heart* (320 gm.) Valves and chambers normal.

Right lung. The lower lobe presented two small patches of whitish consolidation.

The small intestine showed numerous haemorrhagic areas, many of which were ulcerated and covered with slough.

Large intestine. Numerous haemorrhagic areas were present.

Spleen (300 gm.) Enlarged, soft, and pinkish purple.

Kidneys (180 gm. each). The surface was smooth, and pale, the cortex was pale with slight loss of pattern, the pelves were healthy.

Histological findings. The tissues available were lung, intestine, kidney, and skin.

Kidney vessels. Small arteries in the peripelvic tissues showed typical acute phase periarteritis nodosa. The renal vasculature elsewhere was unaffected.

Glomeruli. The normal number was present. The majority showed focal fibrinoid necrosis of the tufts, crescent formation, and endothelial cell proliferation (Plate 16, Fig 9). Some tufts showed focal fibrosis, other glomeruli appeared normal.

No evidence of periarteritis nodosa was found in the lungs, liver, adrenals, brain, spleen, or myocardium

Summary Although this man died in another hospital eight years ago, it is clear from reading the brief history that he had an illness compatible with periarteritis nodosa, the highly suggestive features being a febrile illness with abdominal pain and small gangrenous areas in the bowel, associated with a high pulse-rate throughout, a negative blood-culture, and a uraemic termination. The blood-pressure was normal. The segment of small intestine removed at operation showed the presence of characteristic lesions of periarteritis nodosa, but the subsequent autopsy revealed no further evidence of such lesions in the vessels of other organs. The changes in the renal parenchyma were essentially similar to those of Cases 1 and 2, yet no arteritic changes were seen in the renal vessels. This case demonstrates, firstly, that the organs involved by periarteritis nodosa may be few, in this case intestine and kidney only, and, secondly, that renal parenchymal lesions identical with those seen in the first two cases can occur in the absence of arteritis in the renal vessels themselves.

Case 1 History A man aged 59 years was admitted to hospital on May 30, 1938. The notes unfortunately are very scanty, but indicate that he had been well until March of that year when he had developed weakness of such a degree that he was unable to work. He had been in bed for several weeks with symptoms which included sweating and pyrexia. On several occasions a little blood-stained sputum had been expectorated.

On examination, there was some dullness at the lung bases, especially the right, with diminished breath sounds. The pulse-rate was 120, and the blood-pressure 120/60. The nervous system and abdomen were reported to be normal. The urine, examined on several occasions, contained small quantities of albumin. Throughout his stay in hospital there was fever varying from 99° to 104° F. The man's general condition deteriorated, and he died on June 20, 1938.

X-rays of the chest showed a small patch of consolidation at the left base with probably a small effusion on that side. A blood count showed red cells 3,050,000 per c mm, haemoglobin 44 per cent, colour index 0.71, white cells 16,200 per c mm, differential count, polymorphonuclears 88.5 per cent, other cells 11.5 per cent (eosinophils nil). The blood-urea was not estimated.

Summary of autopsy findings Heart (320 gm.) Fibrinous pericarditis present, but no endocarditis.

Right lung The apex presented appearances suggesting chronic apical tuberculosis. The lower lobes showed scattered small foci resembling tubercles.

Left lung Showed similar appearances at the apex, the lower lobe showed patchy consolidation.

Spleen (400 gm.) Throughout there were scattered greyish foci resembling miliary tubercles.

Kidneys (180 gm. each) The surfaces were smooth, the cortex was swollen, the pattern somewhat obscured, and numerous scattered pin-point haemorrhages were present.

Histological findings The tissues available were kidney, spleen, lung, and thyroid.

Kidney vessels No abnormality except that an occasional afferent arteriole showed early arteriosclerosis.

Glomeruli The normal number was present. The majority showed focal fibrinoid necrosis involving part and sometimes the whole of the tuft (Plate 16, Fig. 7). Epithelial crescents were also present and many showed fibroblastic

Summary This case was unsatisfactory from a documentary point of view, but again there was a mysterious illness with pulmonary and renal features. The blood-pressure was unfortunately not recorded. Pathologically there were lesions in the lungs unequivocally diagnostic of periarteritis nodosa, and the renal parenchymal lesions showed histological appearances similar to those in the preceding cases. In this case, as in Cases 3, 4, and 5 the renal arteries themselves showed no lesions of periarteritis nodosa.

Case 7 History A married woman aged 57 years was admitted on December 20, 1936, and died the next day. Four months previously she had had pains in the head, and three months previously pains in the legs and arms. Two weeks previously she had fallen downstairs and bruised herself, and since then had noticed shortness of breath on exertion. For a few days she had had diarrhoea and vomiting. There was a previous history of Bright's disease 20 years before.

On examination, she was dyspnoeic and looked very ill. Respirations were 40, pulse 136, and temperature 97.8° F. There was pallor, and some oedema of the ankles. The neck veins were engorged. A pericardial friction sound was heard and there were widespread râles in the chest. The abdomen was distended, but no enlargement of the liver and spleen was found. Albumin was present in the urine. The only investigation made during her stay in hospital was a blood count which showed red cells 2,120,000 per c mm, haemoglobin 40 per cent, white cells 46,600 per c mm, differential count, polymorphonuclears 95 per cent, lymphocytes 3.75 per cent, mononuclears 0.5 per cent, eosinophils nil, myeloblasts 0.25 per cent, myelocytes 0.5 per cent.

Summary of autopsy findings *Heart* The weight was not recorded. Fibrinous pericarditis was present, but no endocarditis.

Kidneys (100 gm each) The capsules stripped with some difficulty, exposing a granular surface with distinct whitish-yellow mottlings. The cortex was slightly thickened, and mottled throughout. The demarcation from the medulla was clear.

Histological findings The tissues available were kidney and lung.

Lung No evidence of periarteritis nodosa seen.

Kidney vessels Periarteritis nodosa in acute and subacute phases involved the interlobar, arcuate, and intralobular arteries. The incidence of vascular involvement varied from block to block. In one block the only vessel involved was not demonstrated until after serial sections had been studied (Plate 16, Fig. 11).

Cortex The cortical architecture was almost unrecognizable. There was complete loss of glomeruli and to a lesser extent of the tubules. These had been replaced by numerous granulomatous foci consisting of central necrotic areas infiltrated by polymorphonuclears and lymphocytes, and surrounded by radially arranged fibroblasts and histiocytes (Plate 16, Fig. 12). The foci were separated by a fibrohyaline connective tissue densely infiltrated by polymorphonuclears and lymphocytes. In some foci the remnants of a glomerulus could be identified in the centre. In many foci the radial arrangement of the fibroblasts and histiocytes at the periphery produced a very distinctive periglomerular lesion. The severity and extent of the cortical lesions showed no relationship to the incidence of necrotizing arteritis since they were equally severe in the block which showed but one arterial lesion.

Tubules Many had disappeared, a few groups of dilated tubules were seen near the unaffected glomeruli.

Interstitial tissue In the cortex there was extensive fibrosis severely infiltrated by polymorphonuclears and lymphocytes, but there were some areas

The tubules showed slight dilatation with atrophy of epithelium

Interstitial tissue Scattered foci of lymphocytes were present, some with a periglomerular location

The lungs showed haemorrhagic bronchopneumonia, no characteristic lesions of periarteritis nodosa were seen

Intestine Numerous typical acute phase lesions of periarteritis nodosa were found in the arteries of the mucosa

Skin There was widespread necrotizing arteriolitis, with capillary thromboses and haemorrhages

Pathological summary The lesions in the intestine, skin, and peripelvic tissue indicated periarteritis nodosa, the renal parenchymal lesions were essentially similar to those of the previous cases

Case 6 History A collier aged 35 years was transferred to a medical ward from the Ear, Nose, and Throat Department on May 20, 1939, and died the next day. Notes of his illness are consequently scanty. On April 5 of the same year he had been admitted for bilateral otitis media. Extreme deafness made history-taking difficult. On May 9 he developed pain in the chest with pleural friction. On May 13 he developed severe haematuria. On May 14 signs of pleural effusion had developed and a small quantity of blood-stained fluid was aspirated.

Examination of the heart and abdomen did not reveal any abnormality. The temperature rose occasionally to about 100° F, but was usually normal. The pulse-rate was always rapid, from 90 to 112. The following investigations were made: Pleural fluid, sterile, the deposit showing many red cells, polymorphonuclears, and lymphocytes. A blood count showed red cells 4,500,000 per c mm, haemoglobin 89 per cent, white cells 11,200 per c mm, differential count, polymorphonuclears 79.5 per cent, lymphocytes 14.5 per cent, mononuclears 4.5 per cent, eosinophils 1.5 per cent. Apart from the record of haematuria, there is no note of urine tests. The blood-urea was not estimated.

Summary of autopsy findings *Heart* (400 gm) Enlarged, no endocarditis, haemorrhagic pericarditis.

Both lungs showed fibrinous pleurisy and numerous haemorrhagic infarcts.

Kidneys (380 gm each) The surface was smooth, the cortex thickened, and the pattern somewhat obscured. Demarcation between cortex and medulla was clear. There were pin-point haemorrhages throughout.

The right middle ear contained clear fluid. The left contained exudate, but no frank pus. The left mastoid and petrous bone appeared sclerotic.

Histological findings The tissues available were lung and kidney.

Lung Areas of haemorrhage in which the pulmonary arteries showed necrotizing arteritis were fairly widespread (Plate 16, Fig 10). There was no evidence of pneumonic changes. Occasional arteries showed recent thrombosis. No bacteria were found in the thrombotic or necrotic vessels.

Kidney vessels No abnormality was seen.

Glomeruli A normal number was present. About half showed epithelial crescents and about a quarter focal fibrinoid necrosis of tufts. Others showed varying degrees of focal fibroblastic organization of the tufts. Some tufts contained polymorphonuclears, and endothelial cell proliferation was prominent. Haemorrhages were present in the capsular spaces.

Tubules The convoluted tubules were moderately dilated. Epithelial cells were mainly atrophic.

The interstitial tissue showed oedema and early fibrosis with scattered foci of lymphocytes and small numbers of polymorphonuclears.

The pelvis was healthy.

The right lung showed bronchopneumonia of the lower lobe.

Spleen (220 gm) Numerous infarcts were present

Kidneys (220 gm each) The note states 'typical appearances of early subacute nephritis'

Histological findings The tissues available were spleen, kidney, liver, and myocardium

The kidney vessels showed typical acute phase periarteritis nodosa, involving occasional intralobular arteries, the arcuate and larger arteries were normal, there was no arteriosclerosis

Glomeruli The normal number was present The majority showed varying degrees of fibroblastic obliteration, and fibroblastic organization of crescents A lesser number showed epithelial crescents and foci of fibrinoid necrosis of the tufts A small number showed periglomerular granulomatous lesions resembling those described in greater detail in Case 7 (Plate 17, Fig 13)

Tubules Dilatation with atrophy of epithelium was widespread.

Interstitial tissue Polymorphonuclears, eosinophils, plasma cells, and lymphocytes were present throughout the cortex in large numbers, and tended especially to be aggregated around the glomeruli, there was moderate fibrosis

Spleen Infarcts were present Many arteries showed typical periarteritis nodosa in the acute and early subacute phase The tissue was negative for bacteria

Liver No lesions of periarteritis nodosa were seen

The myocardium showed diffuse interstitial myocarditis, the infiltrating cells were mainly polymorphonuclears No lesions of periarteritis nodosa were seen

Summary The diagnosis of periarteritis nodosa was not made during life, but on reading through the case-notes before the result of histological examination was known The diagnosis is strongly suggested by a mysterious febrile illness in which 'rheumatism', pneumonia, and iritis lead up to death from uraemia, with no evidence of any classical form of nephritis

The lesions in the spleen make the diagnosis of periarteritis nodosa certain, vascular lesions in the kidney are sparse, the degree of glomerular fibrosis is more extensive than in the preceding cases, but some glomeruli showed focal fibrinoid necrosis similar to that in Cases 1 to 6 The splenic infarcts in the absence of endocarditis or other source of emboli, and the absence of organisms in the splenic lesions tend to confirm the diagnosis of periarteritis nodosa The myocarditis in this case is interesting Similar lesions were described in a case of periarteritis nodosa (reported in the *Edinburgh Medical Journal* (1947), 54, 171) at a clinico-pathological exercise, but the diagnosis of associated acute rheumatism was also made

Case 9 History A man aged 52 years was admitted to hospital on June 19, 1937 For 10 months he had suffered from painful redness of the eyes About two months before, he had begun to feel very tired and his eyes became worse He lost appetite and three weeks before was troubled by occasional vomiting About the same time he had noticed shortness of breath on exertion and developed a cough The sputum was occasionally blood-stained

On examination he was obviously pale and ill There were purpuric spots on the abdomen and buttocks Nothing abnormal was noted on examination of the heart The blood-pressure was 155/80 There was slight dullness at the base of the right lung, with râles over both bases The nervous system was normal He died within three days of admission, but during that time the illness was febrile The urine was recorded as containing albumin ++ The blood-urea was 240 mg per 100 c c and there was anaemia with leucocytosis A

of fibrosis relatively acellular, probably representing healed lesions. The medulla was unaffected, there were no demonstrable bacteria in the cortical necrotic foci.

Summary The notes are too brief for any clinical diagnosis to be made in retrospect, but it is to be noticed that the illness started with joint pains, led on to shortness of breath, and ended with diarrhoea, pericarditis, and albuminuria. There was a very high leucocytosis and a severe anaemia. Unfortunately the blood-pressure and blood-urea were not recorded. The only tissues available in this case were lung and kidney, but the renal arterial lesions are unequivocally those of periarteritis nodosa. The periglomerular granulomatous foci were abacterial, and similar lesions in the kidneys and elsewhere have been described in cases of periarteritis nodosa by Wegener (1939), Banowitch, Polayes, and Charet (Case 5, 1942), and Lindsay, Aggeler, and Lucia (1944). The fact that this granulomatous periglomerular lesion was seen in a lesser degree in Cases 8 and 9 indicates that it is to be regarded as a severer manifestation of periarteritis nodosa of the same nature as the necrotizing glomerulitis seen in all the cases of this group. Thus Cases 8 and 9 can be regarded as transition cases connecting Case 7 with the rest of this first group.

Case 8 History A married woman aged 32 years was admitted to hospital on October 11, 1943 and died on October 28. She complained of tiredness and breathlessness on exertion. In May 1943 she had had 'rheumatism', which consisted of pain in the joints of her fingers and hands. This apparently improved, but in June she was admitted to another hospital with pneumonoma. The notes say that she had pain on the right side and signs of consolidation in the right lung, with cough and haemoptysis. A diagnosis of pneumonia was made, but it was noted that she had albumin, blood, and pus in the urine. The blood-urea was 35 mg per 100 c.c. X-rays of the chest showed no sign of tuberculosis. In July she returned to her home, but started with 'rheumatism' again, which consisted of pain in all joints, moving from joint to joint. She did not stay in bed. About that time iritis commenced, first in the right eye and then in the left. Her appetite was poor and she felt very tired, and finally retired to bed at the beginning of October. There was no previous history or family history of importance.

On examination, the pulse-rate was 120 and temperature 100.4° F. She was pyrexial for the first week and had a rigor on October 16. The blood-pressure was 140/80. No physical signs were found in the heart, chest, or abdomen, except for some diminished air entry at the right lung base. The nervous system appeared to be normal and there was no note of the state of her joints. She became progressively weaker and had several attacks of epistaxis. The mode of death was not stated. The following investigations were made. Blood culture, sterile. Erythrocyte sedimentation rate 50 mm in one hour. A blood count showed red cells 2,060,000 per c.mm., haemoglobin 37 per cent, white cells 10,200 per c.mm., differential count, polymorphonuclears 77.5 per cent, other cells 22.5 per cent (eosinophils nil). Other blood counts were similar, the white cells varying from 10,000 to 15,000 per c.mm. The blood-urea was 98 mg per 100 c.c. on admission and gradually rose to 208 mg before death. X-rays of the chest showed slight loss of translucency in the left costophrenic angle. Microscopical examination of the urine showed numerous blood casts and granular casts with frequent red cells and white cells. Urine cultures were sterile. Ward tests of the urine showed albumin throughout. Further readings of the blood-pressure were 125/75, 135/70, and 120/60 on the day before she died.

Summary of autopsy findings Heart (320 gm.) No definite abnormality was present and no endocarditis.

all had haematuria or albuminuria. Despite the constant involvement of the kidneys, not one of the eight cases resembled in its clinical course any recognized form of nephritis. In Case 7 there was a history of 'Bright's disease' 20 years before (no other details of the illness were recorded) and her final illness might perhaps suggest the end-stage of Type 1 nephritis, but for its commencement with 'rheumatic' pains and the leucocytosis of 46,600 per c mm.

Pathological Summary of Cases 1 to 9

Kidneys In most cases both kidneys were enlarged, pale, and the cortical pattern obscured, but there was no gross disturbance of the architecture. Histologically, with the exception of Case 7, the kidneys presented essentially similar lesions, consisting of patchy fibrinoid necrosis of glomerular tufts, with varying amounts of epithelial crescent formation and partial fibrosis of the tufts. Periglomerular inflammatory cell infiltration was a common finding. In Case 7 the predominant lesion was a periglomerular granulomatous focus, and similar lesions were seen to a lesser extent in Cases 8 and 9. Tubular changes consisted usually of dilatation with degrees of atrophy and degeneration of epithelium. Fibrosis of interstitial tissue was variable, and inflammatory cell infiltration usually severe. Typical acute phase periarteritis nodosa involved the renal vessels in four cases, the arcuate arteries were mainly affected, with occasional involvement of vessels larger or smaller than the arcuates. In no case was there endarteritis fibrosa such as occurs in malignant nephrosclerosis, and in only two cases was afferent arteriosclerosis seen, this was slight in both instances and constituted the only histological evidence suggesting that hypertension might have been present during life.

Other organs Typical acute phase periarteritis nodosa was present in organs other than the kidney in all cases except Case 7. Associated lesions included infarcts of the spleen, lung, and liver, foci in the lungs resembling miliary tubercles to the naked eye, intestinal ulcers, and diffuse myocarditis.

The cases in Group A are thus all examples of the microscopic form of periarteritis nodosa in which severe renal damage has been present, the diagnosis having been made in most cases only after histological examination. Similar cases have been reported by Ophuls (1923), Gray (1929), Kountz (1930), Spiegel (1936), and Fahr (1941). The extensive glomerular involvement adequately explains the uraemic termination which may occur in this group. The problem arises as to whether the renal parenchymal changes summarized above can be distinguished from focal embolic nephritis and from malignant nephrosclerosis.

Focal embolic nephritis The resemblance of the glomerular lesions in the kidneys in some cases of periarteritis nodosa to those seen in focal embolic nephritis has been noted by Gohrbandt (1927), Wegener (1939), and Fahr (1941), but the absence of bacterial endocarditis in any of the group, and the presence of typical lesions of periarteritis nodosa both in the kidneys and other organs, serve to eliminate the diagnosis of embolic nephritis. The necessity

blood count showed red cells 3,500,000 per c mm, haemoglobin 48 per cent, white cells 13,500 per c mm, differential count, polymorphonuclears 85 per cent, other cells 15 per cent (cosmophils, not stated) The Wassermann reaction was negative

Summary of autopsy findings The heart (520 gm) was enlarged and there was hypertrophy of the myocardium, no endocarditis was found

The lungs showed bilateral confluent bronchopneumonia

Intestine Two small ulcers with rounded edges were present

The spleen (420 gm) was enlarged and firm with adhesions on the outer surface On section, white mottling on a dark-red background was present

Kidneys (320 gm each) The capsules stripped easily, the cortex was thickened and the pattern obscured, mottled grey and red The report was that the appearances suggested subacute glomerular nephritis

Histological findings The tissues available were spleen, small intestine, and kidney Typical acute phase periarteritis nodosa was found in the vessels of the spleen, small intestine, and peripelvic tissue of kidney

Kidney vessels The arcuate arteries showed degrees of elastosis The intra-lobular arteries showed no definite changes Afferent arterioles showed occasional early hyaline arteriosclerosis

Glomeruli The normal number was present Nearly all were affected The essential lesion was a fibrinoid necrosis of the tuft, either focal or complete Some necrotic glomeruli showed an intense periglomerular polymorphonuclear and lymphocytic infiltration with often radially arranged fibroblasts, presenting the characteristic periglomerular granuloma seen in Case 7 Epithelial crescent formation was also present Haemorrhage into capsular spaces was not infrequent A few completely fibrotic glomeruli were present

The tubules were slightly dilated and epithelial cells somewhat atrophic Red cells, exudate, and leucocytes were present in the lumina

Interstitial tissue Round cell infiltration was diffuse, in addition to periglomerular leucocytic collections Polymorphonuclear infiltration was marked in the medulla, where peritubular haemorrhage had occurred

Summary A peculiar illness starting with conjunctivitis which was resistant to treatment, leading to weakness, pyrexia, chest symptoms, albuminuria, and uraemia, a combination of events which is difficult to ascribe to any condition other than periarteritis nodosa Typical lesions of periarteritis nodosa in the spleen, intestine, and pelvic tissue of the kidney leave no doubt about the diagnosis There is pathological evidence that hypertension may have been present during life (the heart weight of 520 mg, and a degree of renal arteriosclerosis) Its relation to the periarteritis nodosa is not clear, but the glomerular lesions cannot be regarded on morphological grounds as secondary to hypertension

Clinical Summary of Cases 1 to 9 (Group A)

The clinical features of these cases are surprisingly uniform In all the eight cases with clinical records there was an illness compatible with periarteritis nodosa, giving rise to leucocytosis, chest symptoms, and albuminuria Pyrexia was recorded in all but two (terminal) cases In five cases abdominal symptoms were also present, in three, rheumatic pains, and in three cases conjunctivitis or iritis Unfortunately in only four have we a record of both the blood-pressure and the blood-urea All of these showed uraemia with a normal pressure Of the remainder the blood-pressure was normal in two and not recorded in two,

all had haematuria or albuminuria. Despite the constant involvement of the kidneys, not one of the eight cases resembled in its clinical course any recognized form of nephritis. In Case 7 there was a history of 'Bright's disease' 20 years before (no other details of the illness were recorded) and her final illness might perhaps suggest the end-stage of Type 1 nephritis, but for its commencement with 'rheumatic' pains and the leucocytosis of 46,600 per c mm.

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The cases in Group A are thus all examples of the microscopic form of periarteritis nodosa in which severe renal damage has been present, the diagnosis having been made in most cases only after histological examination. Similar cases have been reported by Ophüls (1923), Gray (1929), Kountz (1930), Spiegel (1936), and Fahr (1941). The extensive glomerular involvement adequately explains the uraemic termination which may occur in this group. The problem arises as to whether the renal parenchymal changes summarized above can be distinguished from focal embolic nephritis and from malignant nephrosclerosis.

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for examining many organs in addition to the kidney in attempting an accurate diagnosis of this type of renal lesion is apparent. Fahr (1941) believed that the glomerular lesions in this type of periarteritis nodosa were, in fact, embolic in nature, and suggested that the sources were thrombi in renal artery branches involved by periarteritis nodosa. Our results do not support his opinion, since in only four of the nine cases in Group A were the renal arteries actually the site of periarteritic lesions, and in two of these four the vascular lesions were scanty, whereas the glomerular lesions were diffuse.

Diffuse glomerular nephritis. For the purpose of discussing the differential diagnosis from diffuse glomerular nephritis we propose to adopt the Ellis (1942) terminology. While neither the lesions of Type 2 nephritis, nor those of slowly progressive Type 1 nephritis are likely to be confused with lesions described in Cases 1 to 9, yet the histological picture in the rapidly progressive form of Type 1 nephritis in which epithelial crescent formation is widespread may resemble the lesions found in Group A quite closely, although widespread fibrinoid necrosis of glomeruli is not seen. Moreover, Ellis (1942) stated that intense inflammatory infiltration of the interstitial tissue with 'explosive' lesions of the glomeruli with definite periglomerular inflammatory reaction may occur in some cases of the rapidly progressive form of Type 1 nephritis. This description recalls the appearances seen in Cases 7, 8, and 9, but the question naturally arises as to whether the cases to which Ellis refers were not in fact cases of periarteritis nodosa characterized by the type of renal involvement seen in Cases 7, 8, and 9. The most important finding that enables the diagnosis to be made is the occurrence of typical periarteritis nodosa in the arteries of organs other than the kidneys. Finally, in none of the cases of this group was there a clinical history compatible with Type 1 nephritis, whereas in the majority of the cases the clinical histories were at least suggestive of periarteritis nodosa. Various authors (Löhlein, 1907, Jaffe, 1925, Fishberg, 1927, Russell, 1929, Koch, 1931, and Horn, Klemperer, and Steinberg, 1942) have described the occurrence of arteritis in acute and subacute glomerulonephritis (specially the 'stormy course' of Löhlein), but the question again arises whether these cases were not, in fact, cases of periarteritis nodosa. The clinical and pathological data, specially the histology of organs other than the kidney, necessary for the exclusion of periarteritis nodosa were seldom available in these papers. Russell (1929) mentions necrotizing arteritis with 'purulent infiltration of the vessel walls' occurring in cases of nephritis acris with maximal inflammatory reaction (Type 2, B 2 Cases 64 to 68) which were histologically similar to the cases in our Group A. A study of the scanty clinical data given shows that only two of the five cases suggest nephritis at all. Furthermore, no data of the histological findings in organs other than the kidneys are furnished in the protocols, so that the possibility exists that Russell's group of nephritis acris with maximal inflammatory reaction has included cases of the microscopic form of periarteritis nodosa similar to those described in Group A.

Malignant nephrosclerosis. Numerous authors have admitted the difficulty that may be met with in distinguishing periarteritis nodosa from malignant

nephrosclerosis (Nauheim, 1928, Kountz, 1930, Friedberg and Gross, 1934, Spiegel, 1936, Mallory, 1936, Grant, 1939, Canny, 1940, Fahr, 1941) The characteristic vascular lesions of malignant nephrosclerosis, that is, endarteritis fibrosa of the intralobular arteries and fibrinoid necrosis of the arterioles, were not seen in the nine cases of Group A, although fibrinoid necrosis of the glomeruli was severe and widespread. In malignant nephrosclerosis only a small proportion of glomeruli show fibrinoid necrosis or epithelial crescents (Klemperer and Otani, 1931, MacMahon and Pratt, 1935), whereas in Group A these lesions were widespread. Again, in malignant nephrosclerosis groups of convoluted tubules are often greatly dilated, containing pink-staining casts, such groups of tubules were not seen in cases of Group A. Fibrinoid necrosis of arteries larger than intralobular size with surrounding leucocytic infiltration is rarely seen in malignant nephrosclerosis (Klemperer and Otani, 1931, Fahr, 1941). Hyaline arteriolosclerosis in addition to fibrinoid necrosis of arterioles is usually widespread in malignant nephrosclerosis, but only in two of the Group A cases was arteriolosclerosis present, and then only of slight degree. Final confirmation of the differential diagnosis is presented by the absence of hypertrophy of the left ventricle in eight of the nine cases, and from the clinical point of view by the absence of hypertension during life in the six cases in which the blood-pressure was recorded. It is worthy of mention that Fahr (1941) stated that it is probably just such cases of the microscopic form of periarteritis nodosa that have been reported in the past as examples of diffuse glomerular nephritis without hypertension. We do not, however, claim that hypertension may not occur in these cases, but we would stress the frequent clinical finding of uraemia and a normal blood-pressure.

Clinically, these cases form a group in which a febrile illness suggestive of periarteritis nodosa and unlike any accepted form of nephritis is characterized by chest or abdominal symptoms, leucocytosis, albuminuria, and by a tendency to progress to uraemia without hypertension. Pathologically, vascular lesions characteristic of the acute phase of periarteritis nodosa are found in the kidneys or other organs or both, and the renal parenchymal lesions mainly conform to a distinctive histological picture in which widespread necrotizing glomerular lesions are present in the absence of bacterial endocarditis. A combined study of the clinical and pathological features has provided a satisfactory basis for the separation of these cases of the microscopic form of periarteritis nodosa from rapidly progressive Type 1 nephritis, from focal embolic nephritis, and from malignant nephrosclerosis.

Case Reports, Group B

The following five cases of periarteritis nodosa, in contrast with those of Group A, showed no extensive glomerular lesions in the kidneys.

Case 10 History. A woman aged 26 years was seen in the Out-Patient Department of another hospital on April 15, 1947. She had had intermittent swelling of the ankles for 12 months, relieved by rest. There was no history of

disease of the urinary tract or other illness, except that she had had glaucoma in the left eye. The family history was negative.

On examination the only significant finding was a blood-pressure of 245/155, with some enlargement of the heart. Examination of the urine was negative. She was admitted to hospital on April 21. The blood-pressure was then 270/150, and the notes state that the fundi were normal except for some changes in the calibre of the vessels. She was given thiocyanate treatment. On May 26 she complained of headache, and slight pyrexia was noted. On May 30 there was some bronchial breathing at the root of the left lung, and on May 31 signs of fluid at the right base. On June 9 some blood-stained fluid was aspirated from the right pleural cavity. The next day she was stated to have been in a better condition, but on the following day complained suddenly of feeling ill and after a shivering attack her pulse and colour became poor, she lost consciousness, and died.

The following investigations were made in the course of her illness. The urine contained some albumin, varying from a slight trace to 2 gm per litre. There was an occasional granular cast. Urinary cultures were sterile. The blood-urea was 30 mg. per 100 c.c. and the urea clearance 75 per cent of normal. A urinary concentration test gave a specific gravity of 1.024. An intravenous pyelogram was negative except for slight dilation of the pelvis of the right kidney. X-rays of the chest showed some general cardiac enlargement. A leucocyte count on May 8 showed white cells 10,200 per c.mm., and the differential count was polymorphonuclears 67 per cent, eosinophils 5 per cent, other cells 28 per cent, and on June 4, white cells 16,500 per c.mm. and the differential count was polymorphonuclears 81 per cent, eosinophils 1 per cent, other cells 18 per cent. The erythrocyte sedimentation rate was 15 mm in one hour. The temperature showed rises to 99° or 100° F at first, but was more disturbed later in the illness.

Summary of autopsy findings. Heart Hypertrophy of left ventricle.

The pleural cavities contained about 12 oz. of blood-stained fluid.

Liver Extensive recent subcapsular haemorrhage was present. On section several small vessels containing clot were seen, about 2 mm in diameter.

The pancreas contained an aneurysm 4.5 cm in diameter full of blood clot.

The spleen was enlarged, an aneurysm 2 cm in diameter containing blood clot was present at the hilum.

Kidneys The capsules stripped easily and the surface was smooth. On section cortex and medulla showed no abnormality. In one kidney a small aneurysm containing clot was present in the peripelvic tissue.

Histological findings. Kidney vessels There was no definite arteriosclerosis. The intralobular arteries showed loss of clear demarcation between the coats of the vessel walls, and a number showed variable loss of staining of the internal elastic lamella. Fibroblastic proliferation of the intima was present in variable amounts, but the appearances were not typically those seen in malignant nephrosclerosis. Typical acute periarteritis nodosa was present in small arteries in the peripelvic tissue and a small organizing aneurysm was present in this site. The larger arteries and arcuate arteries were healthy.

Glomeruli No definite abnormality was seen.

Tubules No definite abnormality was seen.

The liver and pancreas contained recently organizing aneurysms typical of periarteritis nodosa.

The spleen showed no aneurysms. The small arteries showed hyalinization of all coats with fibroblastic proliferation of intima and media. No lesions typical of acute phase periarteritis nodosa were seen.

Summary. Clinically, this was a case of severe hypertension in a young woman who gave no history of renal disease. The illness, however, was complicated by pyrexia, leucocytosis, and pleural effusion. Our experience would lead us to suspect periarteritis nodosa in such a case on clinical grounds alone. Pathologically, this case of periarteritis nodosa with aneurysm formation showed no renal parenchymatous lesions, the vascular changes, apart from the aneurysm and the few lesions characteristic of acute periarteritis nodosa in the vessels of the pelvis, were unlike either periarteritis nodosa or malignant nephrosclerosis.

Case 11 History. A youth aged 17 years was admitted to another hospital on July 24, 1946, with a history of epigastric pain and vomiting of one week's duration.

On examination there was some tenderness in the right lower quadrant of the abdomen with pain on deep breathing. The remainder of the examination was negative. The abdomen became distended and a leaking gastric ulcer was suspected. The maximum daily temperature was from 101° to 103° F throughout the illness, and there was no response to penicillin or sulphonamides. On August 14 laparotomy showed firm rubbery glands in the porta hepatis, widespread retroperitoneal lymphadenopathy, some thickening of the duodenum and adjacent pancreas, a slightly enlarged spleen, an adherent indurated patch of omentum in the left paracolic gutter (removed for histological examination), and a normal stomach, gall-bladder, and appendix. The patient's condition gradually deteriorated despite further intensive treatment with penicillin. On August 27 the blood-pressure is recorded as 132/84. He died on September 12. Histological examination of the omentum showed typical periarteritis nodosa involving a vessel of moderate size. The following investigations were carried out during his illness. A blood-culture was negative. The urine contained numerous granular and epithelial casts and red cells. The white cell count was 10,400 per c mm. The erythrocyte sedimentation rate was 50 mm in one hour. The Wassermann reaction was negative. Agglutinations were negative for typhoid, Salmonella, and abortus. The blood-urea was 36 mg per 100 c c.

Summary of autopsy findings. The heart showed minute nodules along the course of the coronary arteries.

The lungs showed some collapse of the right lower lobe, but no other definite abnormality.

The liver was enlarged, and there was one small white nodule on the anterior surface.

Mesentery. Small nodules were present along the course of the mesenteric arteries.

Kidneys. There were multiple yellow infarcts in the cortex of both kidneys involving approximately one-eighth of the total renal substance.

Spleen. One infarct was present.

Histological findings. The heart, mesentery, small intestine, pancreas, adrenals, liver, and voluntary muscle showed acute and subacute phase periarteritis nodosa, involving medium-sized arteries, aneurysms were frequent. In the abdominal lymphnodes no periarteritic lesions were seen, there was pronounced littoral cell hyperplasia of the sinuses.

Kidney vessels. A number of both the interlobar and arcuate arteries showed aneurysms containing blood clot, thrombosis, and arteritis in the healing phase with gross intimal hyperplasia. The intralobular arteries and afferent arterioles were healthy. Recent infarcts in the cortex were associated with the thrombotic vessels.

Glomeruli In between the infarcted areas the parenchyma appeared unaffected, except for an occasional glomerulus showing patchy tuft necrosis

Tubules Slight dilatation of convoluted tubules was present in some areas

Interstitial tissue Apart from perivascular lymphocytic infiltration in the region of the affected vessels, no other abnormality was present

Summary. The diagnosis was made during life by histological examination. The febrile illness with unexplained abdominal pain is compatible with periarteritis nodosa, but there are no characteristic features on which that diagnosis could have been made on clinical grounds alone. Pathologically, this was a case of periarteritis nodosa with widespread aneurysm formation. The renal changes were chiefly those of infarction due to thrombotic vascular occlusion, but the bulk of the kidney parenchyma was apparently healthy. In contrast to Case 10 there were no changes in the intralobular arteries, but occlusive fibroblastic intimal hyperplasia was present in a number of vessels of arcuate size, apart from the thrombotic aneurysms. This case, therefore, presented evidence of vascular lesions due to periarteritis nodosa that might have been a source of renal ischaemia, although there had been no hypertension.

Case 12 History A man aged 25 years had developed continuous frontal headache in February 1946, whilst in Belgium awaiting demobilization. This was followed by colicky pain in the right side of the abdomen. He stated that he had felt a tender lump the size of a golf ball in the right lumbar region. A few weeks later he had noticed that his eyes ached and his vision became blurred, and about this time had had attacks of vomiting, specially in the mornings. The abdominal pain persisted. In the Army he had been involved in two motor accidents, but there was no previous history of illness of any importance. He had never been given a course of sulphonamide treatment. There was no family history of renal disease or hypertension.

On April 25 he was admitted to hospital where hypertension was found (blood-pressure, 200/160). There was bilateral papilloedema with retinal exudates. There was some abdominal tenderness in the right hypochondrium, but no tumour. The heart was not enlarged, and examination of the nervous system was negative. The Wassermann reaction was negative. A blood count showed red cells 4,440,000 per c mm, haemoglobin 80 per cent, white cells 9,800 per c mm, differential count normal. The erythrocyte sedimentation rate was 26 mm in one hour. The cerebrospinal-fluid pressure was 135 mm, and examination negative. The urine contained albumin (3 gm per litre), the maximum specific gravity was 1,006, cultures were negative, and no casts were seen. The urea clearance was 60 per cent of normal. The blood non-protein nitrogen was 45 mg per 100 c c.

Intravenous pyelograms showed poor excretion on the right and left, but no other abnormality was determined. The electrocardiogram was normal. A diagnosis of malignant hypertension was made and he was transferred to the Royal Infirmary under the care of one of us on May 13, 1946.

Examination confirmed the previous findings, but the blood-pressure was now 215/160. The man looked pale and ill. Several points appeared to us to make the diagnosis of malignant hypertension doubtful: the rarity of essential hypertension at this age, the absence of family history, the finding of a slight inconstant pyrexia, the abdominal pain, a leucocytosis on May 14 of 19,500 per c mm (polymorphonuclears 81.5 per cent, eosinophils nil), some tender enlarged lymphnodes in the axillae and groins, and tenderness over the brachial and transverse cervical arteries. On this evidence a tentative diagnosis of periarteritis nodosa was made and a lymphnode and small piece of artery were

removed for biopsy. The report on these was negative. The patient's condition rapidly deteriorated and his blood-urea rose to 222 mg per 100 c c. Death on June 13, 1946, was due to renal and cardiac failure, the course being that of a rapidly progressive malignant hypertension.

Summary of autopsy findings. The heart (380 gm) showed 'concentric hypertrophy' of the left ventricle, the coronary arteries showed many white nodules along their course.

Lungs. Patchy consolidation was present throughout both lungs, the left lung contained a haemorrhagic infarct.

Kidneys. The right kidney weighed 100 gm, on section the cortical pattern was obscured, showing yellow mottling throughout. The left kidney weighed 160 gm, and appeared similar to the right.

There were small aneurysmal dilatations containing blood clot in the vessels of the heart, liver, kidney, spleen, pancreas, stomach, intestine, and mesentery.

Histological findings. Typical lesions of periarteritis nodosa in the acute, subacute, and healed phases were present in the vessels of the myocardium, pancreas, liver, lung, and mesentery.

Kidney vessels. The arcuate arteries showed healing aneurysmal dilatations with and without thrombosis. The walls of the aneurysms consisted of fibrous tissue, and normal components of the arterial wall could not be identified. Other arcuates showed the late healing phase of periarteritis nodosa without actual aneurysm formation. There was dense fibrosis of all coats, and groups of iron-containing phagocytes were present in the adventitia. Varying degrees of destruction and disappearance of the internal elastic lamella had occurred. The intralobular arteries showed two types of lesion. In one there was complete fibrous replacement of all layers of the vessel wall, and iron-containing phagocytes could be seen in the adventitia, and loss of the internal elastic lamella had occurred (Plate 17, Figs 14 and 15). These changes represent the healed phase of periarteritis nodosa. The second type consisted of endarteritis fibrosa similar to that seen in malignant nephrosclerosis. In these vessels the coats of the wall were distinct and the internal elastic lamella was intact. No afferent arteriolar sclerosis or necrosis was seen.

Glomeruli. Many appeared normal, a few showed epithelial crescent formation, a few tuft fibrosis, and others minor degrees of distortion or collapse. No fibrinoid necrotic lesions of tufts were seen.

Tubules. Some groups of convoluted tubules were greatly dilated, containing pink casts. The majority were of normal size, but some areas showed atrophic tubules.

Interstitial tissue. Throughout there were areas of early fibrosis.

Pelvis. No evidence of pyelitis was seen.

Summary. This was a case in which the diagnosis of periarteritis nodosa was tentatively made during life, although the clinical picture was strongly suggestive of malignant hypertension. On pathological examination it proved to be a case of periarteritis nodosa with multiple aneurysm formation in which the affected renal vessels were in the healed or healing phase, with occlusive sclerotic changes, which might have been a primary source of renal ischaemia. In addition, endarteritis fibrosa similar to that seen in malignant hypertension was also seen, these lesions can reasonably be regarded as secondary to the hypertension, which had developed as a result of the earlier occlusive vascular lesions in the renal arteries due to the periarteritis nodosa (Friedberg and Gross, 1934, Canny, 1940).

Case 13 History. A man aged 34 years was admitted to hospital under the care of one of us on July 31, 1946, and died on September 8. In October 1945

he was discharged from the Army on account of 'rheumatoid arthritis'. Notes from another hospital at that time show that he had pain in the hands, arms, and legs, with stiffness, and that there was actual swelling of the first metacarpophalangeal joint in both hands, and spindle-shaped deformity of the fingers. This condition apparently recovered completely, but about the same time loss of energy and insomnia commenced with increasing headache. For a month before admission the headache had been nearly continuous and had given rise to frequent vomiting. There had been some shortness of breath on exertion.

On examination in July 1946 he looked pale and ill. The blood-pressure was 200/148. There were no abnormal physical signs in the chest or abdomen. The nervous system was apparently normal and the optic disks showed no papilloedema. On August 3 he had a generalized convulsion followed by five more fits during the afternoon. This left a transient left facial paralysis. After this his general condition deteriorated rapidly, he was often confused and drowsy. On August 11 the blood-pressure was 208/160, and he complained of blurring of vision. Some retinal haemorrhages were seen, but there was still no papilloedema. Vomiting was frequent at this time. On August 18 the blood-pressure was 210/140, his general condition worse, and nausea, vomiting, and drowsiness developed. The eyesight was very poor, ophthalmoscopic examination showed retinal exudates and detachment of the left retina. There was no pyrexia during his stay in hospital. The following investigations were made: Maximum specific gravity of urine 1.010, albumin constantly present. Blood-urea August 1, 42 mg per 100 c.c., August 30, 94 mg per 100 c.c. A blood count on August 2 showed red cells 5,320,000 per c.mm., haemoglobin 104 per cent, colour index 0.98, white cells 10,200 per c.mm., and differential count, polymorphonuclears 76.5 per cent, lymphocytes 16.0 per cent, and mononuclears 7.5 per cent (eosinophils nil).

Summary of autopsy findings. **Heart.** Left ventricle hypertrophied, no other abnormality.

Lungs. Oedema of lower lobes.

The liver contained an area of necrosis 4 cm. in diameter.

Spleen. Slightly enlarged, firm, and dark red in colour.

Kidneys (140 gm. each). The surfaces presented numerous small dark-red, slightly depressed areas alternating with paler grey areas. The cortical pattern was blurred in parts, and there were alternating areas of pallor and dark-red colour throughout. The demarcation from the medulla was distinct.

Pelvis. Healthy apart from small haemorrhages.

Histological findings. **Kidneys.** The interlobar and arcuate arteries showed severe intimal fibrosis with varying degrees of replacement of the media by fibrosis, and focal loss of the internal elastic lamella (Plate 17, Figs 16 and 17). Perivascular round cell infiltration was variable. One arcuate artery contained organizing thrombus. Adjacent to one arcuate artery which showed intimal hyperplasia and a fibrotic media, there was a small, partly organized aneurysm. These appearances are diagnostic of the healed phase of periarteritis nodosa. The intralobular arteries showed endarteritis fibrosa indistinguishable from that seen in malignant nephrosclerosis. The afferent arterioles showed fibrinoid necrosis with perivascular infiltration, and numerous arterioles showed hyaline arteriosclerosis.

Glomeruli. Some appeared normal, others showed loss of lobulation with increase in intercapillary connective tissue. Others again showed focal fibrinoid necrosis. The normal number of glomeruli appeared to be present.

Tubules. Convoluted tubules were mainly dilated and numerous eosinophilic casts were present.

Interstitial tissue There was patchy fibrosis throughout

Liver The necrotic area was an infarct A nearby artery showed the healing phase of periarteritis nodosa

Myocardium No definite abnormality

Spleen Serial sections of the spleen showed an occasional medium-sized artery whose lumen was filled with collagen fibres, containing several capillaries. The media was just recognizable and there was dense periadventitial fibrosis with round cell infiltration The elastic stain showed rupture and partial disappearance of the internal elastic lamella This appearance is diagnostic of the healed phase of periarteritis nodosa

Summary Clinically, this was a case of severe hypertension in a man of 34 years for which no cause could be found A diagnosis of malignant hypertension was made, but was unsatisfactory as papilloedema never developed and there was the peculiar history of 'rheumatoid arthritis' at the onset of the illness Periarteritis was not suspected during life nor at the post-mortem examination Pathologically, the healed and healing lesions of periarteritis nodosa in the spleen and liver, as well as in the kidney, established the diagnosis of periarteritis nodosa The morphological characteristics seen in malignant nephrosclerosis were present, but there was also unequivocal evidence of healed periarteritis nodosa of the larger renal arteries, with gross diminution of their lumina Thus, as in Case 12, there is a morphological basis for renal ischaemia

Case 14 History A man aged 45 years was admitted to hospital on April 4, 1945, and died on April 12 His complaint was general weakness, with wrist-drop and loss of use of his fingers, and also foot-drop Fourteen weeks before admission he had had pneumonia That was apparently the beginning of the illness and he had never been out of bed since that time A few days before admission he had severe pain in the right side of the abdomen

Examination of the chest, heart, and abdomen was negative There was wrist-drop and foot-drop on both sides with loss of knee and ankle reflexes, but no loss of sensation There was some oedema of both hands The urine contained a trace of albumin on admission, but a much larger quantity later in the illness A diagnosis of polyneuritis was made The blood-pressure was unfortunately not recorded There are no progress notes and the mode of death is therefore not clear One assumes from the result of the investigations that it was from uraemia There was slight fever during the illness

The following investigations were made A blood count showed red cells 2,830,000 per c mm, haemoglobin 50 per cent, colour index 0.89, white cells 18,200 per c mm, differential count, polymorphonuclears 87 per cent, lymphocytes 9 per cent, and mononuclears 4 per cent (eosinophils nil) A fractional test meal showed complete achlorhydria The cerebrospinal fluid was normal The blood-urea was 414 mg per 100 c.c. on April 11

Summary of autopsy findings *Heart* (360 gm) The left ventricle showed no hypertrophy, no endocarditis was seen

Lungs Congestion and oedema were present

Liver (1,900 gm) A large number of small 'abscesses' were scattered throughout

Mesenteric artery A thrombus was present in the pancreatic branches

Kidneys (180 gm and 200 gm) Naked-eye description is lacking

Histological findings *Kidney vessels* Interlobar and arcuate arteries showed extensive fibroblastic intimal proliferation, especially at branch sites, and loss of internal elastic lamella and fibrous replacement of media focally Capillaries could be recognized within the areas of intimal fibroblastic proliferation One

artery, somewhat smaller than arcuate size, showed typical acute phase periarteritis nodosa. Some intralobulars showed endarteritis fibrosa similar to that seen in malignant nephrosclerosis. Others showed fibrinoid necrosis and thrombosis with perivascular leucocytic infiltration. Early organization of thrombus was present in one vessel. A very occasional afferent arteriole showed fibrinoid necrosis and there was no definite arteriolosclerosis.

Glomeruli The normal number was present. Most showed degrees of distortion and collapse. Focal adhesions were fairly common, but only a very occasional epithelial crescent was seen. No fibrotic glomeruli, and no fibrinoid necrotic lesions were found.

Tubules Some were dilated, others small with atrophied epithelium.

Interstitial tissue showed fairly widespread patchy fibrosis, with areas of lymphocytic and polymorphonuclear infiltration.

Liver The 'abscesses' were recently organizing infarcts. No definite evidence of periarteritis nodosa was seen in the sections available, but one vein contained ante-mortem thrombus. Bacteria could not be seen in stained sections of the necrotic areas. The brain and spinal cord showed no abnormality.

Summary Leucocytosis, pyrexia, neuritis, and renal failure with a history of pneumonia and abdominal pain strongly suggests periarteritis nodosa.

The pathological diagnosis of periarteritis nodosa rests on the larger renal arteries showing the typical features of the healed phase of periarteritis nodosa, the presence of a typical acute phase lesion in the kidney, and confirmatory evidence as supplied by the presence of multiple liver infarcts (Pass, 1935) and by the thrombosis in branches of the mesenteric artery, which have occurred in the absence of endocarditis or other demonstrable source of emboli.

As in Cases 12 and 13 there have been obliterative lesions of larger renal arteries due to healed periarteritis nodosa which would have been a cause of renal ischaemia, the intralobular arteries have shown again, as in Cases 12 and 13, endarteritis fibrosa similar to that seen in malignant nephrosclerosis, and may be considered as probably secondary to the hypertension. In this case the blood-pressure during life was not known, so that although there is close similarity in the renal morphology with Cases 12 and 13, the interpretation of the changes in the intralobulars cannot be clinically supported.

Clinical Summary of Cases 10 to 14 (Group B)

In three of these cases severe hypertension dominated the clinical picture. Two of them were seen by us during life. Case 12 was suspected clinically of being periarteritis nodosa for the reasons already given. Case 13 was peculiar in being a severe example of hypertension terminating in renal failure, but without papilloedema. When one adds that the illness commenced with polyarthritis, the discrepancy from typical malignant hypertension becomes more obvious. This case was afebrile when seen by us, all the others had pyrexia from time to time. One of the remaining patients had a normal blood-pressure, in the other it was not recorded. All had albuminuria and three of the five developed uraemia. All had other symptoms, abdominal, thoracic, rheumatic, or neuritic, compatible with periarteritis nodosa. The clinical inference to be drawn from this group seems to be that if hypertension is accompanied by pyrexia, leucocytosis, or other suggestive symptoms, periarteritis nodosa should be suspected. Groups A and B are separated on histological

grounds, but clinically also a distinction can be drawn between them, in that the former showed a tendency to develop renal failure without hypertension, whereas in the latter hypertension was commonly present. Case 11 is an exception in that neither hypertension nor renal failure occurred. In both groups general signs of the disease were found, such as leucocytosis and pyrexia, and symptoms referable to the chest, abdomen, and joints may be seen. All the aneurysmal cases were found in Group B.

Pathological Summary of Cases 10 to 14

Nauheim (1928), Kountz (1930), Schürmann and MacMahon (1933), Mallory (1936), Canny (1940), and Fahr (1941) have stressed the similarity between the renal lesions in some cases of periarteritis nodosa and those seen in malignant nephrosclerosis, and the problem is discussed at some length by Moschowitz (1945). Where aneurysm formation is widespread, the diagnosis of periarteritis nodosa is certain, even though the renal changes may resemble those of malignant nephrosclerosis. Similarly in the microscopic form of periarteritis nodosa where lesions are widespread in the organs, malignant nephrosclerosis has been excluded on this account (Fahr, 1941). The association of malignant hypertension and periarteritis nodosa in the same case has been described by Bau (1934), Friedberg and Gross (1934), Grant (1939), Canny (1940), and Fahr (1941), though none of these authors has attempted a clear separation on morphological grounds of the vascular lesions in the kidney due primarily to periarteritis nodosa from the vascular lesions usually associated with malignant hypertension. In a study of a control group of 18 cases of malignant nephrosclerosis in each of which the clinical history was typical of malignant hypertension, we have found that arteriolonecrosis is practically confined to afferent arterioles and is not associated with perivascular inflammatory cell infiltration, that endarteritis fibrosa is a diffuse lesion of the intralobular arteries, that the larger renal arteries, especially the arcuate arteries, show varying degrees of elastosis, and that in the arcuate and larger arteries, rupture or loss of the internal elastic lamella is never seen, nor was evidence of organization or recanalization of thrombus seen in these vessels. In contrast, in periarteritis nodosa in the acute phase, the vascular necrosis is constantly accompanied by perivascular inflammatory cell infiltration, and commonly medium-sized vessels are involved as well as arterioles. The healed phase of periarteritis nodosa is recognized by focal rupture or loss of the internal elastic lamella, by fibrosis of the media and perivascular tissues in which phagocytes containing iron-pigment may be found (Meyer, 1921), and by severe intimal fibrosis in which capillaries may be present, indicating that organization of thrombus has occurred. Reactive intimal hyperplasia may occur above or below the site of the necrotic lesions, so that serial sections may be needed to demonstrate the diagnostic features of the healed phase.

The application of these criteria to the five cases of Group B has shown that in Case 10 the renal vascular lesions were neither those of periarteritis nodosa

nor malignant nephrosclerosis; in Case 11 only the lesions of periarteritis nodosa were present, while in Cases 12, 13, and 14 the lesions of periarteritis nodosa and of malignant nephrosclerosis co-existed

Relation of Hypertension to Periarteritis Nodosa

Various views have been expressed as to the relation of hypertension to periarteritis nodosa. Thus Kernohan and Woltman (1938) suggested that hypertension depended on the extent of the arterial bed involved by the obstructive effects of the periarteritis nodosa lesions. This view is not supported by our Case 11 where widespread aneurysms with thrombosis were present throughout the body, but no hypertension was present. Fishberg (1939) stated that hypertension does not occur in periarteritis nodosa without extensive implication of the renal arteries. In Case 10 hypertension was severe, yet there was no definite evidence of extensive involvement of the renal arteries by periarteritis nodosa, though in Cases 12 and 13 renal vascular involvement was severe and hypertension present. Gruber (1925) and Spiegel (1936) concluded that there is no consistent correlation between hypertension and any particular type of renal lesion due to periarteritis nodosa. In the cases in Group A glomerular involvement was severe and occlusive vascular lesions absent or minimal. In the six cases in which the blood-pressure was known during life there was no hypertension. In contrast, in the second group of five cases in which widespread glomerular change was not a feature, occlusive vascular lesions of the kidney bore no constant relation to the presence of hypertension. However, in Cases 12 and 13 it is tempting to regard the hypertension as being secondary to renal ischaemia due to the obstructive healed lesions of periarteritis nodosa in the kidney vasculature, the mechanism of the production of the hypertension being analogous to the Goldblatt (1938) mechanism, as Moschowitz (1945) has suggested. This in turn could lead to the hypertensive vascular changes of malignant nephrosclerosis. In this connexion a number of cases has been reported in which hypertension developed in the course of the disease (Kroetz, 1921, Gohrbandt [Case 4], 1927, Kountz, 1930, Fitz, Parks, and Branch, 1939, Herbut and Price, 1945), and occlusive lesions in the larger renal arteries due to healed or healing periarteritis nodosa were present. Thus it is not unreasonable to conclude that in a number of cases in which hypertension complicates periarteritis nodosa a Goldblatt mechanism is involved. In Cases 12 and 13 such occlusive lesions were present and could well have been a primary source of renal ischaemia and hence of severe hypertension. This in turn could have produced the renal vascular lesions of malignant nephrosclerosis. Thus these latter lesions may be regarded as a secondary development, in contradistinction to the primary lesions of periarteritis nodosa.

Summary and Conclusions

1 Fourteen cases of periarteritis nodosa have been described, and divided according to their renal lesions into two main groups

2 Combined clinical and pathological studies have shown that the first group was characterized by the presence of a widespread necrotizing glomerulitis and that the clinical history and course of the diseases were quite unlike either Type 1 or Type 2 nephritis, or malignant hypertension

3 In the second group the renal findings were more varied, and bore no close relation to the presence or absence of hypertension, but in two cases with severe hypertension there was evidence of healed lesions of periarteritis nodosa involving larger branches of the renal artery, which may have acted as primary causes of renal ischaemia

4 Our findings in both groups indicate that a careful histological study of other organs in addition to the kidneys is necessary to exclude the diagnosis of periarteritis nodosa in any case in which the renal histological picture may resemble that of focal embolic nephritis, Type 1 nephritis, or malignant nephrosclerosis. Of no less importance in achieving a correct diagnosis is a close clinico-pathological correlation of the available data, and we would stress that cases with renal failure or hypertension occurring in a pyrexial illness should be especially suspect

5 In conclusion, the nosological implications of this study need consideration. Work by Masugi and Isibasi (1935), Rich and Gregory (1943), and Cavelti and Cavelti (1945) has suggested that there is a fundamental similarity in the pathogenesis of nephritis and periarteritis nodosa, and it may be questioned whether it is any longer justifiable to continue to attempt to separate the two conditions. We must concede that cases may be met in which a definite dividing line is difficult to draw. Nevertheless, it is possible, as we have shown, to separate on both clinical and pathological grounds a substantial number of cases of the microscopic form of periarteritis nodosa from diffuse nephritis. We believe that, in the present state of our knowledge, this separation will assist rather than retard the elucidation of the problems of the classification of renal disease, and of the correlation of clinical findings with morbid histology in this field.

We wish to express our thanks to our colleagues at the Manchester Royal Infirmary for permission to use their clinical records, to Dr G. J. Crawford for the material and autopsy reports of Cases 10 and 11, and to Professor S. L. Baker for helpful criticism.

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FIG 1 Case 1 Kidney Arcuate artery showing segmental fibrinoid necrosis of the wall with intense leucocytic infiltration Typical acute phase lesion of periarteritis nodosa (Haemalum and eosin, $\times 90$)



FIG 2 Case 1 Kidney The upper glomerulus shows focal fibrinoid necrosis, the lower shows epithelial crescent formation The tubules are dilated and there is fibrosis and leucocytic infiltration of the interstitial tissue (Haemalum and eosin, $\times 90$)

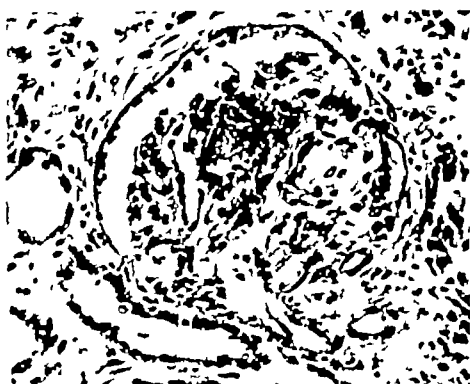


FIG 3 Case 1 Kidney A higher magnification of the upper glomerulus in Fig 2 showing the focal fibrinoid necrotic lesion, and periglomerular leucocytic infiltration (Haemalum and eosin, $\times 200$)

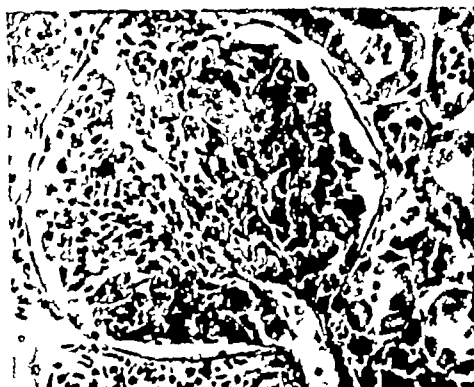


FIG 4 Case 2 Kidney Glomerulus showing focal fibrinoid necrosis, leucocytic infiltration, and swelling of the endothelial cells The afferent arteriole appears unaffected (Haemalum and eosin, $\times 250$)



FIG 5 Case 3 Intestine An artery in the submucosa showing acute phase periarteritis nodosa The adjacent vessel is unaffected (Haemalum and eosin, $\times 34$)



FIG 6 Case 3 Kidney The upper glomerulus shows focal fibrinoid necrosis and epithelial crescent formation the lower shows complete necrosis Periglomerular leucocytic infiltration is present The tubules are lined by atrophic epithelium (Haemalum and eosin, $\times 160$)

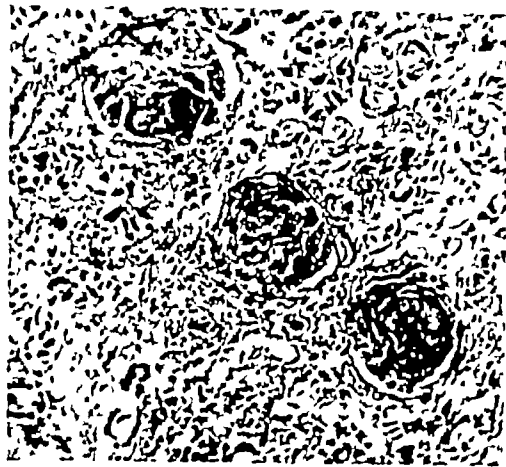


FIG 7 Case 4 Kidney Glomeruli showing varying amounts of fibrinoid necrosis of the tufts (Haemalum and eosin $\times 140$)



FIG 8 Case 4 Spleen Acute phase periarthritis nodosa Thrombosis in the vessel lumen has occurred, there is intense perivascular leucocytic infiltration (Haemalum and eosin $\times 135$)

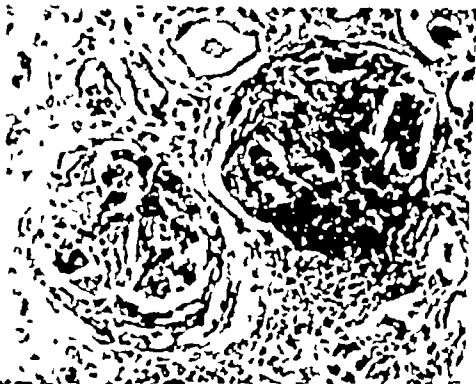


FIG 9 Case 5 Kidney Glomeruli showing focal fibrinoid necrosis and epithelial crescent formation (Haemalum and eosin $\times 200$)



FIG 10 Case 6 Lung A pulmonary vessel showing dense leucocytic infiltration of the wall The surrounding alveoli contain red cells (Haemalum and eosin, $\times 120$)



FIG 11 Case 7 Kidney Arcuate artery showing segmental destruction

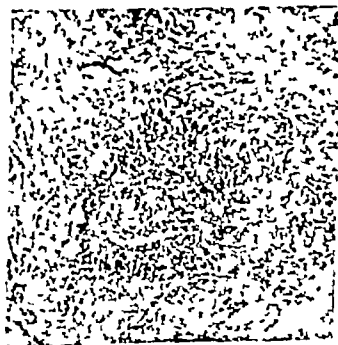


FIG 12 Case 7 Kidney A glomerular granulomatous reaction



FIG 13 Case 8 Kidney Glomerulus (top left) showing a periglomerular granulomatous lesion, the remaining two show stages of fibroblastic obliteration (Haemalum and eosin, $\times 120$)



FIG 14 Case 12 Kidney Healed phase periarteritis nodosa of intra-lobular arteries, showing gross fibrous obliteration (Haemalum and eosin $\times 110$)



FIG 15 Case 12 Kidney Consecutive section to Fig 14 The internal elastic lamella is intact in the vessel at the top right, but the vessels below show partial (left) and complete (right) loss of the elastic lamellae (Weigert's elastic and van Gieson's stain $\times 110$)



FIG 16 Case 13 Kidney Healed phase periarteritis nodosa involving an interlobular artery, showing severe intimal fibrosis, segmental fibrosis of media, and slight perivascular leucocytic infiltration (Haemalum and eosin, $\times 105$)



FIG 17 Case 13 Kidney Showing segmental loss of internal elastic lamella at site of fibrotic media (Weigert's elastic and van Gieson's stain $\times 105$)

THE TOXIC EFFECTS OF CALCIFEROL¹

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IN 1924, Hess and Weinstock, and Steenbock and Black, independently showed that lipid-containing foods, when irradiated with ultraviolet light, acquired anti-rachitic properties. The work of Rosenheim and Webster (1925) in this country, Hess and Weinstock (1925) in the United States of America, and Windaus and Hess (1927) in Göttingen, showed the anti-rachitic principle to be irradiated ergosterol, which Askew, Bourdillon, Bruce, Jenkins, and Webster (1930) isolated in crystalline form and named calciferol. Other products than calciferol are formed in the process, such as lumisterol, tachysterol, and toxisterol, to which the toxic effects of calciferol were attributed. Harris stated in 1932 that pure vitamin D₂, or calciferol, might account entirely for the toxicity of crude irradiated ergosterol. This was confirmed by Steck, Deutsch, Reed, and Struck in the dog (1937), and in man by Reed (1938). The toxic effects in animals of large doses of irradiated ergosterol were reported by Kreitmair and Moll in 1928. In the same year the occurrence of clinical hypervitaminosis D in human beings was first published by Hess and Lewis.

Calciferol has been used in high dosage for the treatment of rickets (Hess and Lewis, 1928, Klausner-Cronheim, 1930, Tu-Tunji, 1931, Zelson, 1940, Wolf, 1943, Krestin, 1945 *a, b*), tetany (Hess and Lewis, 1928, Reed, 1934, Steck, Deutsch, Reed, and Struck, 1937, Eaton, 1946), inanition (Thatcher, 1931, 1936, Ross and Williams, 1939), hay-fever and asthma (Rappaport and Reed, 1933, Reed, 1934, Steck, Deutsch, Reed, and Struck, 1937), arthritis of various types (Wyatt, Hicks, and Thompson, 1936, Holbrook and Hill, 1936, Vrtiak and Lang, 1936, Steck, Deutsch, Reed, and Struck, 1937, Abrams and Bauer, 1938, Steinberg, 1938, Slocumb, 1942, Freyberg, 1942, Danowski, Winkler, and Peters, 1945, Freeman, Rhoads, and Yeager, 1946, Covey and Whitlock, 1946, Paul, 1946, Bevans and Taylor, 1947, Kaufman, Beck, and Wiseman, 1947, Magnuson, McElvenny, and Logan, 1947), psoriasis (Freyberg, 1942), fractured bones (Tumulty and Howard, 1942), lupus vulgaris and other tuberculous conditions (Charpy, 1943, 1946, Dowling and Thomas, 1945, 1946, Faniello, 1946, Debré, Thieffry, Brissaud, and Trelu, 1946, Meyer, Gaulher, and Desgrez, 1946, Macrae, 1946, 1947, Anderson, 1947, Feeny, Sandiland, and Franklin, 1947, Hohmann and Beening, 1947), and in normal subjects (Hess and Lewis, 1928, Reed, 1934, Steck, Deutsch, Reed, and Struck, 1937). Most of these authors have reported toxic symptoms (Table I). Nevertheless, Reed

¹ Received March 9, 1948

TABLE I
Summary of Published Series

<i>Author(s)</i>	<i>Number of cases</i>	<i>Disease</i>	<i>Age</i>	<i>Preparation of vitamin D</i>	<i>Daily dose (u)</i>	<i>Daily dose per kg body weight (approx)</i>	<i>Period of treatment</i>	<i>Toxic symptoms</i>	<i>Renal impairment</i>
Hess and Lewis (1928)	1	None	12-9 months	Irradiated ergosterol	50,000	800	8 weeks	1	Yes
	11	None			5,000-50,000	7,000-10,000	1-12 weeks	1 (10 %)	Yes
Klausner Cronheim (1930)	3	Two with no disease	41-7 months	Vigantol	10,000-50,000	1,500-8,000	0-15 days	3 (100 %)	Yes
Tu-Tunji (1931)	1	One rickets	2 years	Vigantol	100,000	33,000	1 day	Yes	Yes
Vrbak and Lang (1930)	20	Rickets	23-50 years	Vioosterol	150,000-250,000	2,300-3,500	3 to 10 months	Nausea in all	In a few
		Arthritis	?	Vioosterol	200,000-300,000	3,000-4,000	7 6 months	8 (20 %)	No data
Wyatt, Hicks, and Thompson (1936)	38	Arthritis	?						
	2	Rheumatic fever							
Steck, Deutsch, Reed, and Struck (1937)	555	Post operative tetany, hay fever, asthma, arthritis, miscellaneous, and normal subjects	?	Vitamin D in corn oil	1,500-3,000	1,500-3,000	87 days	5 (100 %)	No data
	123				3,000-5,000	3,000-5,000	60 days	25 (45 %)	
	70				6,000-7,000	6,000-7,000		18 (14 6 %)	
	16					8,000-15,000	10 days	11 (15 7 %)	
	4					15,000-25,000	10 days	3 (18 8 %)	
						25,000-35,000	10 days	1 (20 %)	
Abrams and Bauer (1938)	18	Rheumatoid and other types of arthritis	17-64 years	Vitamin D2 in oil or propyl glycol	40,000-300,000	600-4,000	7 weeks to 10 months	13 (71 %)	Not investigated
Stenberg (1938)	40	Arthritis	32-70 years	Not specified	100,000	2,300	'Weeks to 1 1/2 years'	None	No data
Ross and Williams (1939)	4	No diagnoses given	8-14 months	Irradiated ergosterol	20,000-10,000	2,000-4,000	Several months	4 (100 %)	Yes in 3
Snyder and Squires (1940)	23	Arthritis	8-65 years	Ertron	200,000-400,000	3,000-6,000	4 to 18 months	8 (34 %)	No data
Freyberg (1942)	30	Arthritis	?	Ertron	200,000-300,000	3,000-4,000	'Months'	8 (22 %)	
	1	Arthritis	?	Ertron	50,000	750	?	1	Yes
	8	Osteoarthritis or fibrositis	?	Ertron	200,000-300,000	3,000-4,000	?	1 (12 %)	
	14	Psoaritis	?	Ertron	300,000	3,000-4,000	'Months'	1 (7 %)	

(1934) wrote—'there need be little apprehension about the administration of amounts ranging up to 150,000 i u daily for indefinite periods' Reed, Struck, and Steck, writing in 1939, put the threshold for intoxication for human subjects at 20,000 units per kg of body-weight per diem for most preparations Steinberg (1938) felt that the toxicity of massive doses of vitamin D had been over-emphasized, but a more recent paper (Debré, Thieffry, Brissaud, and Trellu, 1946) showed how dangerous this therapy may be for children After reviewing the results of many workers, Snyder and Squires (1940) came to the conclusion that most patients could tolerate doses of 200,000 to 400,000 i u daily Dale, Marble, and Marks (1932) showed that with massive doses of calciferol, the serum calcium and phosphorus levels were raised Bauer, Marble, and Claflin (1932) demonstrated an increased urinary excretion of calcium and phosphorus, but a decreased faecal excretion Calciferol increases the absorption of calcium and phosphorus (Albright and Sulkowitch, 1938), and lowers (faecal) phosphorus excretion owing to diminished calcium excretion (Nicolaysen, 1937) Calciferol, however, increases the urinary excretion of phosphorus (Albright and Sulkowitch, 1938) Thus the serum levels for calcium and phosphorus will be determined by the summation of the action of calciferol on urinary and faecal excretion If renal damage occurs, phosphate retention is often present and the final level of serum calcium and phosphorus is determined by the interaction of these various factors In normal serum, part of the calcium is protein-bound and part is diffusible The latter fraction exists as ionic calcium and as calcium complexes, possibly citrate and phosphate

The Administration of Calciferol in High Dosage

The present investigation concerns 200 out-patients suffering from the following diseases lupus vulgaris (167 cases), sarcoidosis (12 cases), Bazin's disease (7 cases), tuberculosis verrucosa cutis (5 cases), scrofuloderma (3 cases), tuberculous lymphadenitis (2 cases), tuberculide (2 cases), follicular lupoid (1 case), and dermatitis herpetiformis of childhood (1 case) Of these patients, 119 were female and 81 male Fig 1 shows the age incidence of the series All patients received two pints of milk daily in addition to their normal rations Calciferol was given daily by mouth in tablet form (tablet Ostein high-potency (Glaxo), each tablet containing 50,000 i u) in doses varying between 50,000 and 150,000 i u Fig 2 shows the mean daily dose per kg of body-weight taken during the course of treatment, and Fig 3 the total dose per kg of body-weight The period of treatment varied between one and 21 months (mean 8 ± 3.94) Daily ultraviolet-light therapy was given for some months during calciferol treatment to eight (23 per cent) of the patients who became toxic and to 45 (29 per cent) of the non-toxic patients

Apart from clinical, and in some cases radiological and electrocardiographic examinations, the following biochemical investigations were undertaken Total serum-calcium determinations were made by Clarke and Collip's (1925) modification of the Kramer-Tisdall method The diffusible calcium was determined by

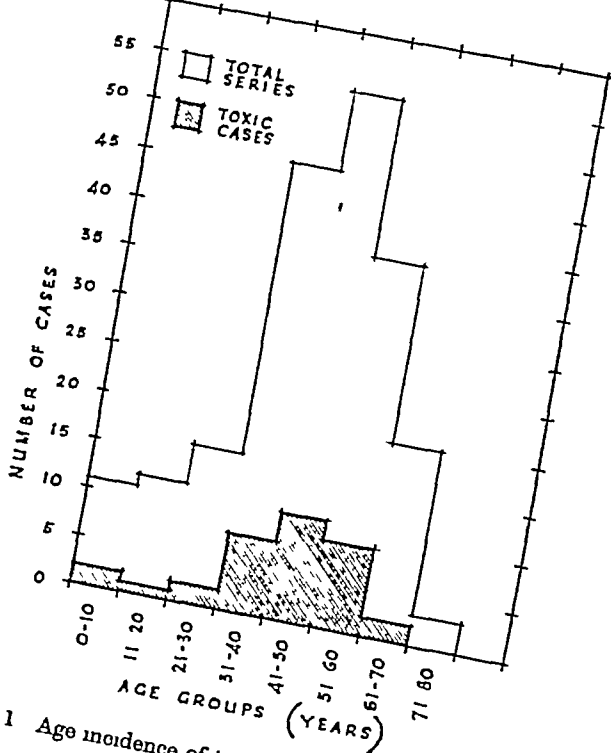


Fig 1 Age incidence of total series and toxic group

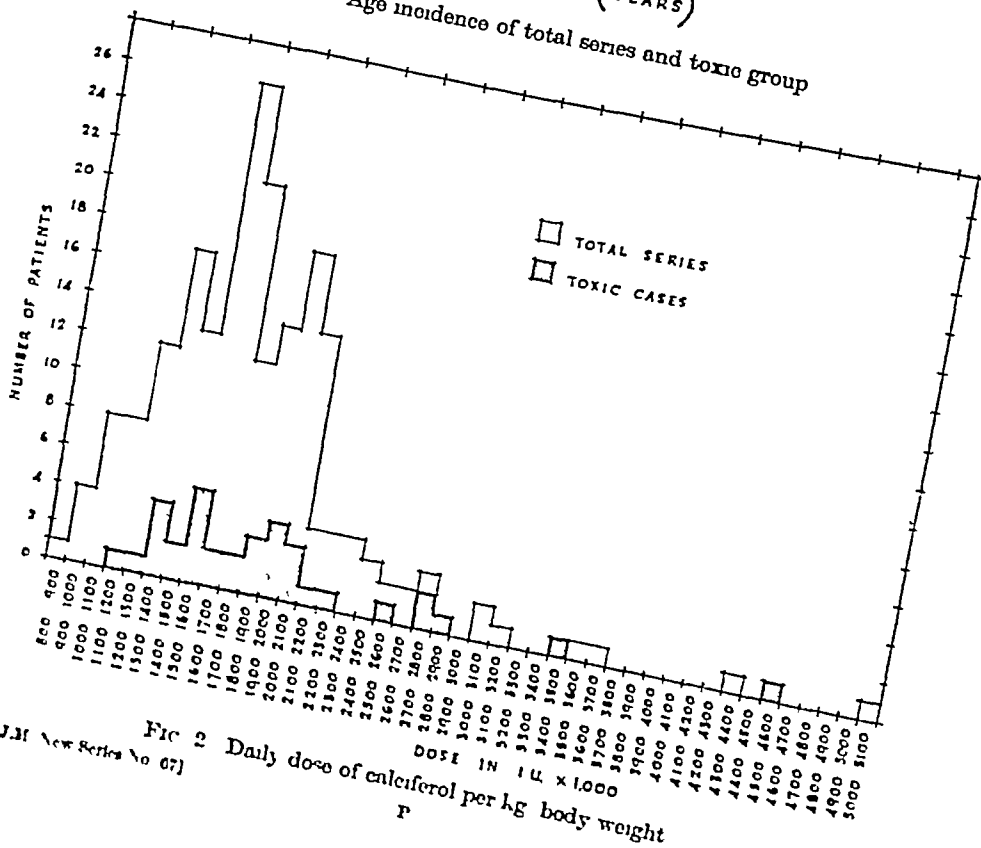


Fig 2 Daily dose of calciferol per kg body weight

the ultrafiltration technique of Updegraff, Greenberg, and Clark (1926), and the serum-protein determination by the copper-sulphate technique of Van Slyke, Phillips, Dole, Emerson, Hamilton, and Archibald (1945). The ionic calcium was estimated by Dr. Neil in some patients, using his modification of the frog-heart technique of McClean and Hastings (1935). The method of Briggs (1922) was used in the estimation of inorganic phosphorus. The renal function of some

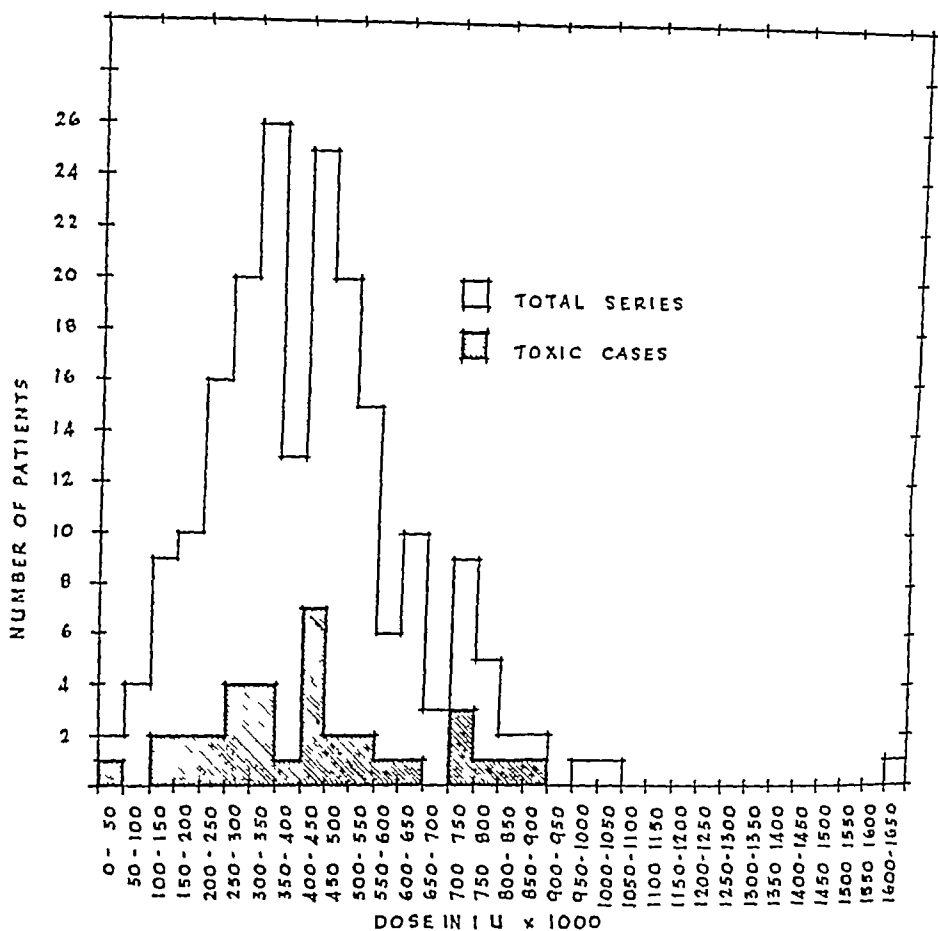


FIG. 3 Total dose of calciferol per kg body-weight

patients was investigated by the urea clearance test as described by Möller, McIntosh, and Van Slyke (1928).

We also carried out experiments to determine the results of calciferol therapy in rabbits with renal damage, two groups of animals were used. In one group the rabbits received two injections of 2 mg uranyl acetate in 5 c.c. of saline, subcutaneously, at three days' interval. The other group received the same dose of uranyl acetate, but, in addition, 50,000 i.u. of calciferol were given daily by mouth until death. In both groups death usually occurred within five days of the commencement of treatment, and a post-mortem examination was

made. In addition, a group of three rabbits given calciferol (50,000 i u each daily by mouth) and a group of three control rabbits were investigated for biochemical changes in the serum.

The Toxic Effects of Calciferol

The term 'biochemical toxicity' is used to indicate a marked departure from the normal ratio of diffusible to total calcium. This is not necessarily accompanied by clinical manifestations. In the present series of 200 patients, 38 (19 per cent) complained of toxic symptoms, but of these only 35 will be considered here from the biochemical standpoint as three were admitted to other hospitals and could not be investigated by us. Of the 35 patients, 23 were female and 12 male. The number of toxic cases in each age-group is shown in Fig. 1. The total dose of calciferol producing toxicity varied between 1.4 and 35 million i u at the onset of symptoms. The actual daily dose being taken at the time of onset of toxic symptoms was, in the 35 toxic patients, 100,000 or 150,000 i u or 2,080 units per kg of body-weight ($S D \pm 402$). In the 'biochemically toxic' patients (28 cases) the mean daily dose per kg of body-weight at the time was 2,270 ($S D \pm 285$). In the remaining non-toxic group (134 patients) the mean of the highest daily dose taken, expressed in units per kg of body-weight, was 1,837 ($S D \pm 567$). It may be concluded that the size of the daily dose per kg of body-weight is of importance in determining whether or not toxicity occurs.

The following symptoms were complained of by the toxic patients

Thirst	22 cases	Intolerance of noise	5 cases
Anorexia	18 "	Loss of weight	3 "
Vomiting	16 "	Excitability	3 "
Tiredness	15 "	Photophobia	2 "
Malaise	15 "	Rhinorrhoea	2 "
Nausea	15 "	Metallic taste in mouth	1 "
Headache	13 "	Dizziness	1 "
Constipation	7 "	Sleeplessness	1 "
Abdominal pain	7 "	Deterioration of memory	1 "
Polyuria	6 "	General ill health	1 "

Abdominal pain was so severe in two of these patients and in the three patients discarded from the series for lack of investigation, that they were admitted to hospital as abdominal emergencies and three of them underwent laparotomy. Common symptoms of toxicity are anorexia, nausea, vomiting, and constipation or diarrhoea. Epigastric discomfort has been described by Abrams and Bauer (1938) and Macrae (1940), and abdominal pain by Rappaport and Reed (1933) and Tumulty and Howard (1942). Dryness of the mouth and thirst is common, occasionally a sweet taste in the mouth (Slocumb, 1942) and sensitiveness of the teeth to temperature changes (Freeman, Rhoads, and Yeager, 1946) or pains in the jaws and teeth (Bicknell and Prescott, 1946). An initial sense of well-being is followed by malaise, depression, and occasionally excitability (Charpy, 1946). This symptom, together with restlessness,

TABLE II
Details of Fatal Cases

<i>Case</i>	<i>Sex</i>	<i>Age</i>	<i>Body weight (kg)*</i>	<i>Dose per dcm</i>	<i>Dose per kg body weight per dcm (i u)</i>	<i>Duration of therapy</i>	<i>Preparation of calciferol</i>	<i>Primary disease</i>	<i>Renal function</i>	<i>Necropsy findings</i>
Putzchar (1929)	M.	5½ months	7.58	2.2 mg irradiated ergosterol	1,000 (approx)	96 days	Vigantol	Scleroderma, marasmus, and cystitis	No data given	Calcification of the tubular epithelium, basement membrane, and renal interstitial tissue, none elsewhere
Thatcher (1931)	M	18 months	7	10 c c 'twice the curative dose'	Not known	5 months	Irradiated ergosterol emulsion	None (not gaining weight)	'Blood urea 90 mg (about 3 times normal)' Albuminuria	Calcification of renal tubules, none elsewhere
Spies and Hanzal (1933)	?	'Young adult'	?	4 to 18 million i u	Assuming the body-weight to be 65 kg	9 days	Irradiated ergosterol	Miliary tuberculosis	No data given of any of these cases	The patients were clearly dying before the exhibition of vitamin D commenced. All organs examined, but no evidence of calcification found
	?	"	?	"	61,500 to 276,000 given to each case	16 days	"	"		
	?	"	?	"		16 days	"	'Metastatic carcinoma'		
	?	"	?	"		25 days	"			
Thatcher (1936)	M	11½ months	7.5	400-1,200 i u	50 to 160	4 months	Cod liver oil	Not gaining weight	Albuminuria (trace)	Calcification of renal tubules, none elsewhere
Ross and Williams (1939)	M	8-14 months	?	20,000 to 40,000 i u	2,000 to 4,000	'Several months'	Ostogen (irradiated ergosterol)	None	No data given	Calcification of media of arteries, cardiac muscle, alveoli of lungs, bronchi, kidneys (especially tubules) extensive metastatic calcification
Vollmer (1941)	F	3 years	11.3	86,000 i u (mean of 3 doses in 28 days)	7,080 (mean over 26-day period)	26-day period	Crystalline vitamin D3 (intramuscularly)	Lymphatic leukaemia	Urino normal	Doses of 1 million, 600,000, and 900,000 i u given 26, 13, and 7 days, respectively, before death. No calcification found
	F	19 months	6.8	140,000 i u (mean of 2 doses in 9 days)	22,000 (mean over 9 days of 2 doses)	9 day period	Tuna fish-liver oil concentrate (intramuscularly)	Miliary tuberculosis	Urino normal	Doses of 1 million and 260,000 i u given 9 and 3 days, respectively, before death. No signs of calcification found.

Wolf (1917)	M	1-3 months	33	300,000 i u	85,000	12 days	Ertron	Meningo coele and spina bifida	No data	Calcification of renal tubules
Hauer and Freyberg (1916)	F	12 years	753	100,000 to 500,000 i u	1,724 to 8,620	1 year at least	Vitamin D Plastasol	Duodenal ulcer	Albuminuria (trace)	Renal vessels, tubules, and glomeruli, myocardium, and media of arteries calcified
Mulligan (1916)	M	11 years	78	Unknown but large	Unknown but large	6 months	Unknown	None	Albumin, casts, and red cells in urine	Calcification of endothelium of many capillaries and of intima of small arteries and veins of myocardium, lungs, and of renal tubules and vessels
Kaufman, Beck, and Wismar (1917)†	F	63 years	760	150,000 to 200,000 i u	2,500 to 3,393	14 months	Ertron	Rheumatoid arthritis	Low specific gravity urine Persistent albuminuria Raised blood urea nitrogen	Calcification of renal artery, tubules, and glomeruli, myocardium, lung alveoli, one parathyroid, pancreas, joints of extremities, subcutaneous tissue

* Where the weight is not given in the original paper, the average weight for that age and sex is taken, and marked ?

† It is assumed that this case is the same as that reported by Bevans and Taylor (1917)

was prominent in three of our patients. Apathy, drowsiness, and coma may occur as late symptoms (Debré, Thieffry, Brissaud, and Trelu, 1946). Psychic disturbances (Hess and Lewis, 1928, Ravina, 1936, Covey and Whitlock, 1946) and a confused memory and insomnia are described. Headache and, less frequently, giddiness (Rappaport and Reed, 1933, Reed, 1934, Steinberg, 1938, Feeny, Sandiland, and Franklin, 1947), amblyopia (Charpy, 1946), presbyopia (Meyer, Gaulier, and Desgrez, 1946), numbness and tingling of the extremities (Rappaport and Reed, 1933), tightness across the occiput with tenderness (Reed, Struck, and Steck, 1939), disturbed muscular co-ordination and a dull aching in the muscles (Reed, 1934), and diffuse aches and pains (Debré, Thieffry, Brissaud, and Trelu, 1946) are recorded. Polyuria, with nocturia, are common symptoms. Bicknell and Prescott (1946) and Reed, Struck, and Steck (1939) noted aphrodisiac effects. Running of the eyes and nose (Macrae, 1947), profuse sweating (Bicknell and Prescott, 1946), and a productive cough have been noted (Kaufman, Beck, and Wiseman, 1947). Many of the patients complaining of toxic symptoms had a dull, tired expression and activity was resented. In the severe cases, the facies suggested slight dehydration. The tongue was dry and coated. Loss of weight has been reported by many authors (including Hess and Lewis, 1928, Klausner-Cronheim, 1930, Steck, Deutsch, Reed, and Struck, 1937, Macrae, 1947). The blood-pressure readings of our toxic cases were not significantly altered, though Debré, Thieffry, Brissaud, and Trelu (1946) and Reed (1934) found a rise in blood-pressure as a late change in toxic patients who had continued treatment with calciferol. In two of our patients, without toxic symptoms, necrotic granulomatous lesions appeared in the skin and slowly cleared after treatment was discontinued.

Special investigations. Albuminuria occurred in four toxic patients, while glycosuria was present in one of these and seven other toxic cases, and in seven patients with no toxic symptoms. In all these the abnormality disappeared shortly after calciferol was stopped.

Glucose tolerance tests in five patients with glycosuria showed a renal type of curve.

The erythrocyte sedimentation rate was not determined. Macrae (1946, 1947) found it raised in the early stages of toxicity. A rise is often to be found in untreated lupus vulgaris.

X-rays of kidneys and limbs showed no change in 30 patients treated, of whom 15 had been toxic. The total dose of calciferol at the time of radiography varied between 5.2 and 53.2 million i.u. (mean 18.1 ± 9.4 million). Eaton (1946) reported calcification of peripheral arteries in one case, and Feeny, Sandiland, and Franklin (1947) calcification of the abdominal aorta and pelvic arteries. Debré, Thieffry, Brissaud, and Trelu (1946) demonstrated rarefaction of bones and calcification of soft tissues and lungs after massive doses of calciferol in children.

Agduhr and Stenström (1929, 1930 a, b) fed animals with cod-liver oil and found electrocardiographic changes which they correlated with histological degeneration in conducting tissue. Jundell and Stenström (1931) with cod-liver

oil and vigantol produced changes of the same nature in children under one year of age. Tumulty and Howard (1942) described a negro aged 22 years with multiple fractures, who on 750,000 i.u. of irradiated ergosterol daily for 17 days developed toxic symptoms with impaired renal function, hypercalcaemia, and in the electrocardiogram a PR interval of 0.38 sec which slowly decreased after stopping vitamin D. In a fatal case of vitamin-D intoxication, described by Bauer and Freyberg (1946) (see Table II), the electrocardiogram showed a PR interval of 0.28 sec, and a QRS interval of 0.10 sec. At necropsy one week

TABLE III
Results of Electrocardiography

Case	Age	Sex	Calciferol total dose (million i.u.)	Blood pressure	Heart rate (per minute)	PR interval (sec.)	QT interval (sec.)	Total serum-calcium (mg per 100 c.c.)	Diffusible serum-calcium (mg per 100 c.c.)	Remarks
188	42	M	9.5	120/80	46	0.18	0.40	11.5	7.1	Normal ECG. Sinus bradycardia
35	51	F	30.1	110/70	88	0.17	0.38	10.5		Normal ECG.
172	49	F	5.6	140/75	37	0.24	0.52	12.5	8.2	ECG no different from that before calciferol
185	49	F	15.0	145/85	73	0.23	0.39	12.5	8.8	Left axis deviation. Toxic symptoms
45	53	F	14.3	170/100	86	0.17	0.36	10.7	7.3	ECG normal. Had stopped calciferol 11 weeks before owing to toxic symptoms
155	56	F	36.8	125/70	91	0.19	0.36	11.3	6.4	Left axis deviation, ECG otherwise normal
60	46	F	35.0	160/90	71	0.20	0.37	13.8	7.8	Toxic symptoms 2 weeks later. ECG normal
186	66	F	6.3	150/90	68	0.21	0.40	10.7	6.8	Toxic 1 month previously. ECG normal except for left axis deviation

later, myocardial degeneration with calcification was found. An infant described by Jelke (1946) showed hypercalcaemia, renal damage, and marked changes in the electrocardiogram. The QT interval was short (0.21 to 0.22 sec) and T high, broad, and positive. The total serum-calcium was 13.8 mg per 100 c.c. Another case, reported by Skatvedt (1947) (see Table I) showed raised blood-urea nitrogen and hypercalcaemia (19.8 mg per 100 c.c.) and a plateau-like T wave. The QT interval was normal. In the present series the electrocardiogram of eight patients having calciferol therapy was studied. The results are shown in Table III. It will be noted that the electrocardiographic tracing was found to be normal in every patient, except for left axis deviation in two, and bradycardia in two others, changes not brought about by calciferol. The QT interval in all was within normal limits and no abnormalities of the QRST complex were found. Of these eight patients, four had suffered from toxic symptoms and all had taken large doses of calciferol. It may be concluded that there is no consistent change produced in the electrocardiogram by calciferol, in toxic or non-toxic subjects, though defects in conduction, as shown

TABLE IV
Urea Clearance Tests

Case	Age (years)	Sex	Weight (kg)	Calciferol total dose (million u)	Clearance test		Period after calciferol stopped (weeks)	Renal function impaired
					1st hour (%)	2nd hour (%)		
Toxic Cases								
11	37	M	66	30.2 (18.2)*	59	54	6	Yes
13	57	F	66	32.0 (1.0)	69	77	13	No
19	10	M	29	8.4 (2.5)	62	64	9	Yes
					44	40	34	Yes
					55	57	44	Yes
25	53	F	44	25.9 (7.7)	95	101	11	No
48	40	F	56	31.5 (nil)	107	81	4	No
53	46	F	83	32.4 (nil)	49	54	27	Yes
55	19	M	48	35.7 (5.2)	95	103	15	No
56	41	F	53	10.1 (5.3)	60	56	14	Yes
					67	64	27	Yes
					56	66	50	Yes
60	46	F	47	11.2 (2.8)	72	78	0	No
63	37	M	71	53.2 (nil)	69	73	10	No
64	58	M	65	7.7 (4.2)	64	70	0	?
111	52	F	70	14.7 (1.4)	65	59	29	Yes
122	39	F	61	24.1 (4.9)	57	67	0	Yes
				31.1†	42	46	20	Yes
133	51	F	70	32.9 (2.1)	72	72	3	No
137	60	F	65	28.7†	47	44	10	Yes
					40	46	15	Yes
					97	79	43	No
144	55	F	50	25.9 (23.8)	52	50	16	Yes
					99	96	44	No
173	43	F	60	8.4 (7.0)	40	44	10	Yes
					44	43	19	Yes
177	50	M	66	17.1†	83	77	0	No
179	8	M	22	16.1 (1.4)	70	66	49	No
185	49	F	66	14.0†	42	48	minus 1	Yes
				15.0 (0.5)	36	33	5	Yes
186	66	F	52	5.4 (nil)	60	57	9	Yes
'Biochemically Toxic' Cases (Symptomless)								
23	48	M	62	32.9 (10.5)	61	67	0	Yes
45	53	F	56	15.7 (nil)	51	51	2	Yes
					76	74	9	No
155	56	F	55	47.6	60	58	minus 8	Yes
				56.0 (8.4)	55	49	0	Yes
					52	50	13	Yes
165	35	F	65	8.4 (nil)	79	90	4	No
184	8	F	23	17.8 (nil)	41	43	0	Yes
198	26	M	67	22.5 (nil)	80	77	0	No
Non toxic Cases								
89	36	F	56	25.2	76	70	0	No
159	20	F	55	6.3	92	98	21	No
187	43	F	48	9.8	80	71	16	No

* Dosage taken after onset of toxic symptoms, or first biochemical evidence of toxicity

† See illustrative cases for details

Note No impairment of renal function is considered to be present when the urea clearance is 70 to 130 per cent in one hour

by a lengthened PR interval, have been described. Shortening of the QT interval (or the duration of ventricular systole) may rarely be found.

Urea clearance tests were carried out on 30 patients in the series (see Table IV). Of these, 21 were suffering or had suffered from symptoms of toxicity, six had shown serum-calcium changes indicating 'biochemical toxicity' without symptoms, and three patients were not toxic. Of the 21 patients with toxic symptoms, 12 showed impairment of renal function (with urea clearance less than 70 per cent during both the first and second hours of the test). Of the eight patients who showed no impairment of renal function, several had taken little or no calciferol after the onset of symptoms, or had been investigated for renal efficiency some weeks after stopping calciferol therapy. Some patients (e.g., Nos 19, 53, 56, 111, and 122) showed marked impairment of renal function although little calciferol had been taken after the onset of symptoms, or though many weeks had elapsed after stopping calciferol before the urea clearance tests were carried out. Of the six patients who were 'biochemically toxic', four showed renal impairment. One patient, in addition, No 185, showed impairment while 'biochemically toxic', but developed symptoms one week later, and is shown in the group with toxic symptoms. Of the 16 patients who showed impairment of renal function, a repetition of the urea clearance test was carried out in 10, and some improvement was noted in five. For example, Case 19, 34 weeks after calciferol was stopped, showed a urea clearance of 44 per cent in the first hour, which 10 weeks later had risen to 55 per cent. On the other hand, Case 56 showed no improvement in renal function almost a year after the cessation of calciferol therapy. Cases 137 and 144 showed a return to normal after 10 months. It appears from the results in Table IV, that impairment of renal function is less likely to occur if the treatment is discontinued at the onset of symptoms.

Biochemical Investigations After treatment with calciferol there is an increase in serum-calcium. This rise is not marked in patients without toxic symptoms, and may be within normal limits, but is marked in those with clinical evidence of toxicity (Table V). The diffusible serum-calcium increases

TABLE V
Results of Serum-Calcium Estimations

	Number of estimations	Total serum-calcium	Diffusible calcium	Ionic calcium (20 cases)
		(mg per 100 c.c.)		
Untreated cases	20	10.9 ± 0.17	5.6 ± 0.13	4.3 to 5.2
Treated cases	160	11.9 ± 0.20	6.0 ± 0.04	5.0 ± 0.1
Toxic cases	30	13.2 ± 0.39	8.2 ± 0.09	5.2 to 5.6

with treatment, and this rise is remarkably uniform. The greatest rise is observed in the clinically toxic patients. Among the treated non-toxic patients there are some with diffusible calcium levels as high as those found in the toxic group. The lowest diffusible calcium level found in the latter group was 7.5 mg

per 100 c c , and this level has been taken as indicating the imminence of a toxic state The level of ionic calcium shows no significant variation The large difference between diffusible and ionic calcium levels has been equated with the development of a calcium steroid complex The steroid has been isolated in small quantities from the blood of rabbits given large doses of calciferol, and further studies on its nature are in progress We regard the estimation of

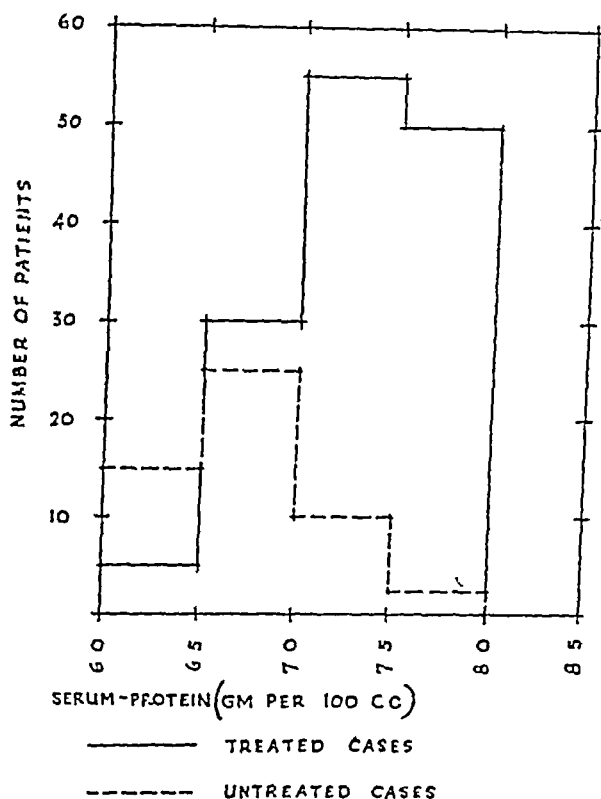


FIG 4 Distribution of serum proteins

diffusible serum-calcium as being the surest method of determining the onset of calciferol toxicity

The serum-protein is increased during treatment with calciferol in high dosage (Fig 4)

The estimation of serum inorganic phosphorus reveals a comparatively wide variation which appears to bear no relationship to the change in diffusible calcium level (Figs 5 and 6)

Estimation of blood-urea nitrogen was carried out at regular intervals in every patient in the present series Table VI gives the results obtained in the same patients as those for whom the results of calcium estimation are given in Table V The results demonstrate that no significant alteration in blood-urea

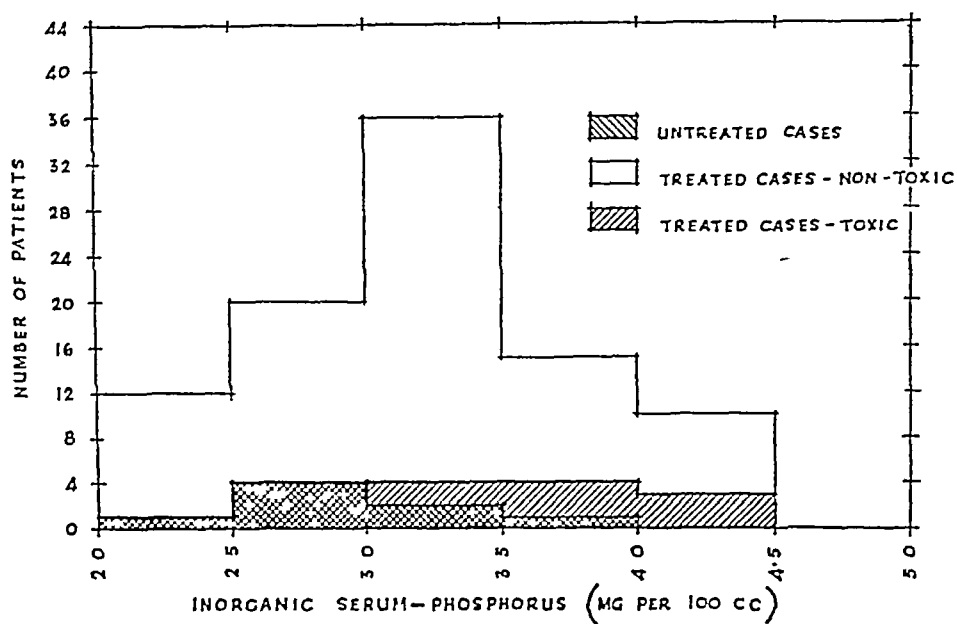


FIG 5 Distribution curve showing the results of inorganic phosphorus estimations

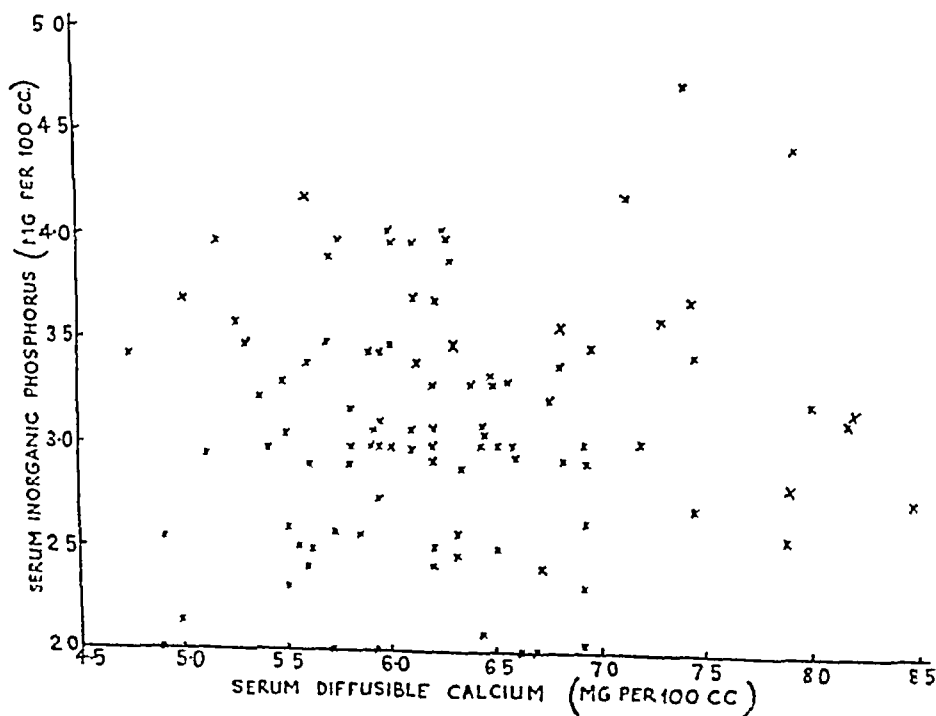


FIG 6 Scatter diagram showing the relationship between serum diffusible calcium and serum inorganic phosphorus

nitrogen follows treatment with calciferol, but the difference between the blood-urea nitrogen levels of toxic and non-toxic patients is significant. However, the variation in individual values is so great that in any given subject a moderate rise in blood-urea nitrogen is not of itself firm evidence of toxicity.

The serum alkaline phosphatase estimated in six patients was within normal limits.

Experiments on rabbits Table VII shows the results of serum-calcium estimations in three rabbits given calciferol (50,000 i u by mouth) daily for two

TABLE VI

Results of Blood-urea Nitrogen Estimations

	Number of estimations	Blood-urea nitrogen (mg per 100 c c)	Variation
Untreated cases	25	25.1 \pm 1.9	17.4 to 32.4
Treated cases	64	25.4 \pm 0.7	17.0 to 33.2
Toxic cases	25	32.8 \pm 4.0	24.0 to 50.4

TABLE VII

Results of Serum-calcium Estimations in Rabbits

	Rabbit 1	Rabbit 2	Rabbit 3
Total serum calcium (mg per 100 c c)			
Before treatment	15.0	15.6	16.2
After 2 months' calciferol	17.8	20.3	17.1
Diffusible serum calcium (mg per 100 c c)			
Before treatment	6.0	8.7	6.5
After 2 months' calciferol	10.2	12.8	10.2

months. Three rabbits given uranyl acetate in addition died before any change was noted in the total or the diffusible calcium. Three control rabbits showed no change in serum diffusible calcium. Histological examination of kidneys of rabbits treated with calciferol showed tubular degeneration with calcification, whilst examination of those treated with uranyl acetate and calciferol showed massive calcification. The kidneys of rabbits treated with uranyl acetate alone showed glomerular and tubular damage but no calcification. In rabbits treated with calciferol, tubular degeneration was slight compared with that seen after treatment with uranyl acetate.

Illustrative Case Reports

No. 19. A boy aged 10 years, weight 29 kg, suffering from lupus vulgaris, was given 100,000 i u of calciferol daily from July 17, 1946. In September 1946 red blotches appeared on his face and forearms, he had attacks of pain in the forehead and jaw lasting about 10 minutes and recurring every day or two. During the attacks he was hypersensitive to sound and trembled. Calciferol was stopped on October 7, 1946 (total dose 8.4 million i u), and the symptoms disappeared during the following two weeks. The results of investigations are summarized on p. 219.

Date	Serum-calcium (mg %)			Blood urea nitrogen (mg %)	Urea clearance tests (%)		Urine	Remarks
	Total	Diffusible	Ionic		1st hour	2nd hour		
Nov 12, 1946	16.2	8.6	6.6	43.6		.	Normal	Now feeling well Calciferol stopped 5 weeks before
Dec. 11, 1946	11.7			28.2	.		Normal	
Mar 5, 1947	12.5	7.0		27.0	.		Normal	
June 3, 1947	10.0	6.0		28.2	.		Normal	Urea clearance test 34 weeks after calciferol stopped
June 26, 1947					44	40	Normal	
Sept 2, 1947				.	55	57	Normal	
								Still impairment of renal function 44 weeks after calciferol stopped

No 48 A man aged 40 years, weight 56 kg, suffering from lupus vulgaris, took 100,000 i u of calciferol daily from August 29, 1946, to September 19, 1946, when the dose was increased to 150,000 i u daily. He continued on this dose until April 11, 1947 (total dose 31.6 million i u). Before calciferol was stopped he had headaches and thirst. His symptoms disappeared within two weeks of stopping calciferol. The results of investigations are as follows:

Date	Calciferol daily (i u)	Serum-calcium (mg %)		Serum-protein (gm %)	Blood urea nitrogen (mg %)	Urea clearance tests (%)		Urine	Remarks
		Total	Diffu- sible			1st hour	2nd hour		
Oct 28, 1946	150,000	11.7			20.3			Normal	Feeling well
Jan 22, 1947	150,000	11.1			23.8			Normal	
Feb 18, 1947	150,000	11.6			24.5			Normal	Feeling well
Apr 11, 1947	Stopped	14.3	8.0	7.35	25.6			Normal	Toxic symptoms
May 8, 1947						107	81	Normal	Feeling well
July 31, 1947		10.8	7.5	7.55	24.4	..		Normal	

No 122 An unmarried woman aged 39 years, weight 61.5 kg, suffering from lupus vulgaris, started calciferol on September 28, 1946 (100,000 i u daily). The dose was increased to 150,000 i u on December 16, 1946. On March 5, 1947, she vomited and complained of nausea and loss of appetite. There was no thirst and no pain, but she stopped calciferol and her symptoms disappeared within three days. She started calciferol again (100,000 i u daily) on April 10, 1947, and stopped on May 31, 1947. The results of the investigations are shown on p. 220.

Date	Serum-calcium (mg %)		Serum-protein (gm %)	Blood urea nitrogen (mg %)	Urea clearance test (%)		Remarks
	Total	Diffu- sible			1st hour	2nd hour	
Dec 16, 1946	11.1			24.8			
Feb 12, 1947	13.7			26.2			
Mar 6, 1947	13.2	7.8	7.0	20.2			Toxic symptoms Calciferol stopped
Apr 10, 1947	11.2	7.3	7.0	20.7			Feeling well Calciferol resumed
May 20, 1947					57	64	Calciferol stopped, May 31, 1947
Aug 12, 1947	10.3	5.8		27.5			X ray of kidneys normal
Oct 16, 1947					42	40	
Oct 21, 1947	10.6	5.3	7.6	24.7			Urine normal throughout

No 137. A married woman, aged 49 years, weight 65 kg, suffering from lupus vulgaris, took 50,000 i u of calciferol daily from March 10, 1946, to Sept 26, 1946, when the dose was raised to 150,000 i u. Three weeks later (Oct 16), having suffered from malaise, nausea, vomiting, and constipation for several days, she stopped taking the tablets. Her symptoms disappeared after one week, and on Nov 26, 1946, she recommenced calciferol therapy, taking 50,000 i u daily until Dec 13, 1946, and 100,000 i u daily from that date until April 1, 1947, when toxic symptoms returned. She complained of thirst and anorexia, which disappeared in two weeks. The results of the investigations are as follows:

Date	Calciferol daily (i u)	Serum-calcium (mg %)		Serum-protein (gm %)	Blood urea nitrogen (mg %)	Urea clearance test (%)		Remarks
		Total	Diffu- sible			1st hour	2nd hour	
Oct 16, 1946	Stopped							Toxic symptoms
Oct 23, 1946	(Total dose 12.9 million)	10.0			42.5			X-ray kidneys normal
Nov 12, 1946	.	12.4			37.0			Feeling better
Nov 26, 1946	50,000							Feeling well
Dec 13, 1946	100,000	13.1	8.7	6.6				Feeling well
Jan 12, 1947	100,000	12.7	5.9	7.6	33.4			Feeling well
Apr 1, 1947	Stopped	14.6	9.3	7.3	37.7			Thirsty, anorexia
Apr 22, 1947	(Total dose 11.5 million)							Feeling better
June 12, 1947						47	44	Feeling well
July 14, 1947						40	46	Feeling well
Oct 21, 1947		11.3	6.5		29.6			Feeling well

No 177 A man aged 50 years, weight 66 kg, suffering from Boeck's sarcoidosis, commenced treatment on May 19, 1946 (100,000 i u daily) On March 31, 1947, owing to thirst and malaise he stopped treatment for a week On September 23, 1947, treatment was stopped again as he was 'biochemically toxic', though symptoms had not recurred The urine was normal throughout The results of investigation are as follows

Date	Serum-calcium (mg %)		Serum-phosphorus (mg %)	Serum-protein (gm %)	Blood urea nitrogen (mg %)	Urea clearance tests (%)		Remarks
	Total	Diffusible				1st hour	2nd	
Nov 5, 1946	10.5				24.8	.	.	
Jan 28, 1947	11.0	6.8		7.5	30.2	.	..	
Mar. 25, 1947	13.9	7.4		8.1	30.1		..	Toxic symptoms Stopped calciferol Mar 31, 1947
June 17, 1947	10.7	5.9	3.0	7.4	30.4	.	.	Feeling well Calciferol therapy recommenced May 20
June 24, 1947					..	83	77	
Sept 23, 1947	13.2	7.9	3.5		27.7	.		Biochemically toxic No symptoms Calciferol stopped
Nov 4, 1947	12.3	7.4	2.7		24.1	.		Feeling well

No 185 An unmarried woman, aged 49 years, weight 66 kg, suffering from lupus vulgaris, was given 100,000 i u of calciferol daily from April 16, 1947, until May 20, 1947, when the dose was increased to 150,000 i u daily She stopped treatment on August 2, 1947 (total dose 15.0 million i u), owing to malaise, nausea, and vomiting The symptoms disappeared after a few days The urine was normal throughout The results of investigation are as follows

Date	Calciferol daily (i u)	Serum-calcium (mg %)		Serum-phosphorus (mg %)	Serum-protein (gm %)	Blood urea nitrogen (mg %)	Urea clearance tests (%)		Remarks
		Total	Diffusible				1st hour	2nd	
Apr 16, 1947	100,000		.	.		27.3	.		Feeling well
May 21, 1947	150,000	10.6	6.5	4.1	8.4	31.3			Feeling well
June 17, 1947	150,000	10.7	6.4	3.1	7.5	32.0	.		Feeling well
July 15, 1947	150,000	12.5	8.8	3.6	7.5	37.4	.		'Biochemically toxic'
July 24, 1947	150,000					.	43	48	
Aug 2, 1947	Stopped					.			Toxic three days
Sept 2, 1947		11.2	6.2	2.9	7.6	30.8			Feels better
Sept 8, 1947				.			36	33	X ray of kidneys normal
Mar 4, 1948				.	..		48	42	

No. 186 A widow aged 66 years, weight 52 kg, who suffered from Boeck's sarcoidosis, was given 100,000 i.u. of calciferol daily from June 16, 1947, until August 7, 1947 (total 5.1 million i.u.) She stopped treatment because of weakness, malaise, headache, dizziness, muddled memory, nausea, and excessive thirst. She was sleeping badly and suffering from nose-bleeding. She resumed on September 20, 1947. The results of investigations are as follows:

Date	Calciferol daily (i.u.)	Serum-calcium- (mg %)		Serum-phosphorus (mg %)	Serum-protein (gm %)	Blood-urea nitrogen (mg %)	Urea clearance (ccs %)		Remarks
		Total	Diffusible				1st hour	2nd hour	
June 16, 1947	100,000	10.0	4.8	2.0	7.5	23.0			Treatment started
July 14, 1947	100,000	10.2	6.5	4.2	7.8	22.6			Well. Occasional thirst
Aug 7, 1947	Stopped								Toxic symptoms one week
Sept 20, 1947	100,000								Feeling well
Oct 6, 1947	100,000	10.7	6.8	2.3	6.4	24.2	60	57	Well. ECG (Table III)
Oct 14, 1947	100,000	10.4	5.8	3.2	6.2				Urine, a few red cells and hyaline casts

The Diagnosis of Toxicity

The diagnosis of toxicity rests upon the history, symptoms, and biochemical investigations. The physical signs are not usually helpful in diagnosis. Thirst, anorexia, and tiredness are common, and are usually the earliest symptoms to appear. The estimation of diffusible serum-calcium appears to give the most constant indication of toxicity or impending toxicity, and a diffusible serum-calcium content of 7.5 mg per 100 cc, or higher, shows such a state, particularly if a parallel rise in total serum-calcium has not occurred. The estimation of the total serum-calcium is not a reliable indication of toxicity (Reed and Thacker, 1931, Reed, 1934, 1938, Abrams and Bauer, 1938, Slocumb, 1942, Debré, Thieffry, Brissaud, and Trellu, 1946, Dowling and Thomas, 1946, Hohmann and Beening, 1947), though we found a significant rise in our group of toxic patients. The blood-urea nitrogen content is also unreliable. Anderson (1947) considered a rise in serum phosphate a more reliable indication of early intoxication than the calcium level, but he presented no data and our results are at variance with this view. A fall in alkaline serum phosphatase is considered by Powell, Pearsall, and Wigley (1948) to be an early indication of toxicity. A change in the alkaline serum phosphatase level was not found in the few estimations carried out in the present investigation, nor in the three cases reported by Curtis, Taylor, and Grehan (1947). A rise in plasma-protein content usually takes place and is probably the basis for the increased erythrocyte sedimentation rate found by Macrae (1946, 1947) which we do not consider to be significant. The diagnosis of toxicity may present difficulties when the doctor does not know that the patient has been treated with calciferol. A variety

of diagnoses may be suggested, such as pyrexia of unknown origin, carcinoma coli, acute abdominal emergency, and uraemia

The Incidence of Toxic Symptoms

The incidence of toxic symptoms found in various series of cases is shown in Table I. The influence of such factors as the nature of the original disease, the age of the patient, the dosage and preparation of calciferol used, the mode of intake, the period of treatment, the diet, and the closeness of observation may not always have received sufficient consideration, and should be borne in mind in their interpretation. In our cases of lupus vulgaris and those treated by Dowling and Thomas (1946), Feeny, Sandiland, and Franklin (1947), Hohmann and Beening (1947), and Macrae (1947) the dosage and period of treatment were similar. The daily dose per kg of body-weight varied from 750 to 5,100 i.u. The total number of cases under treatment and the percentage of these with toxic symptoms were 38 and 20 per cent, 150 and 23 per cent, 87 and 28 per cent, 30 and 50 per cent, and 200 and 19 per cent, respectively. It is clear that with this dosage of calciferol (in the treatment of lupus vulgaris) about 20 per cent of patients will develop toxic symptoms. With higher doses, as used in the United States of America in arthritis, a larger proportion is affected. Other factors than dosage and the duration of treatment which affect the incidence of calciferol intoxication may be briefly mentioned.

Other factors influencing toxicity We do not agree with the American authors who consider that the ingestion of calcium (in milk) predisposes to calciferol intoxication (Steinberg, 1938, Reed, Struck, and Steck, 1939, annotation, *J. Amer. med. Ass.*, 1946). Additional calcium was given by Wyatt, Hicks, and Thompson (1936) and Feeny, Sandiland, and Franklin (1947) without apparent increase in the incidence of toxicity. The French workers, following Charpy (1946) in the treatment of lupus vulgaris, gave extra milk and did not consider that the incidence of toxicity was increased. Shelling (1930) found that rats fed on a diet with a high phosphorus content suffered from the toxic effects of large doses of calciferol more rapidly than those on other diets. It is doubtful whether the results of animal experiments should be applied to human beings, for there is increasing susceptibility to calciferol in the following order—rat, dog, man, rabbit (Steck, Deutsch, Reed, and Struck, 1937).

Individual susceptibility to calciferol may be marked. Many writers mention cases in which toxic symptoms have developed after comparatively small doses, and in the present series toxicity occurred with a daily dose of 1,130 i.u. per kg of body-weight for 12 months, and in five patients after total doses of 1.4 to 3.1 million i.u.

Children are not more resistant than adults to vitamin D, but have higher requirements (McCance, 1947). Pre-existing disease may affect susceptibility. In rickets and other states of vitamin D deficiency susceptibility is diminished (Debré, Thieffry, Brissaud, and Trellu, 1946) and very large doses of calciferol may be given without toxic effects. It has been given in single doses of 200,000

to 600,000 i u to infants who were premature or rachitic or liable to rickets owing to malnutrition (Zelson, 1940, Wolf, 1943, Krestin, 1945 a, b) Krestin (1945 b) found no toxic manifestations in such infants until 2 million i u had been given

The association of renal disease with rickets may predispose to intoxication, and doses which are usually tolerated may produce metastatic calcification (Wolf, 1943). In adults, renal disease increases susceptibility to the toxic effects of calciferol (Reed, Struck, and Steck, 1939)

Resistant rickets and a similar syndrome in adults with osteomalacia were discussed by Albright, Burnett, Parson, Reifenstein, and Roos (1946) McCance (1947) reported such a case and reviewed the relevant literature Individuals with very high resistance may require so much vitamin D that they suffer from the toxic effects of the vitamin (Mackay and May, 1945) Fluctuations in the requirement of vitamin D may occur and McCance and Widdowson (1942, 1943) have shown that the season of the year and other factors may affect the response of normal persons to vitamin D

The vehicle in which the vitamin is administered and the route by which it is given appear to affect the incidence of toxicity Debré, Thieffry, Brissaud, and Trellu (1946) found that alcoholic solutions were more toxic than oily ones, specially when given by mouth, and Gounelle, Sassier, and Marche (1947) stated that calciferol given by the intramuscular route did not produce toxic effects in dogs Similar negative results were found in human beings by Gounelle (1947), but not by Charpy (1946) and Fanielle (1946)

The purity of the vitamin may be of importance, and the toxic effects caused by vigantol during the years 1928 to 1931 may have been due to a high content of toxisterol (Bills, 1935)

The Pathological Effects of Calciferol Intoxication

The effect of calciferol intoxication on renal function appears to be of great importance Albuminuria, described by many authors (Hess and Lewis, 1928, Klausner-Cronheim, 1930, Tu-Tunji, 1931, Debré, Thieffry, Brissaud, and Trellu, 1946, Covey and Whitlock, 1946, Freeman, Rhoads, and Yeager, 1946, Paul, 1946, Feeny, Sandiland, and Franklin, 1947), occurred in some of our patients but was transient, clearing within a few days of cessation of treatment with calciferol The renal glycosuria found in some of our patients does not appear to have been described previously as a complication of calciferol therapy An inability to concentrate urine was noted by Paul (1946) and the excretion of urine of low specific gravity has been mentioned by other authors The presence of granular or hyaline casts and red blood corpuscles in the urine was reported by Hess and Lewis (1928), Klausner-Cronheim (1930), Tumulty and Howard (1942), Bauer and Freyberg (1946), Covey and Whitlock (1946), and Hyde and Hyde (1947) The blood-urea nitrogen content was found to be raised by Slocumb (1942), Tumulty and Howard (1942), Danowski, Winkler, and Peters (1945), Paul (1946), Charpy (1946), Debré, Thieffry, Brissaud, and

Trellu (1946), Freeman, Rhoads, and Yeager (1946), Jelke (1946), Kaufman, Beck, and Wiseman (1947), Magnuson, McElvenny, and Logan (1947), and Hyde and Hyde (1947) Fanelle (1946) stated that half his patients with lupus vulgaris on calciferol therapy were uraemic, but gave no data. We found a raised blood-urea nitrogen content in our toxic patients. Reduction of urea clearance in toxic cases was mentioned by Tumulty and Howard (1942), Freeman, Rhoads, and Yeager (1946), Covey and Whitlock (1946), and has been demonstrated in many of our patients (Table IV). Some workers (Danowski, Winkler, and Peters, 1945, Covey and Whitlock, 1946, Debré, Thieffry, Brissaud, and Trellu, 1946, Freeman, Rhoads, and Yeager, 1946, Hyde and Hyde, 1947, Frost, Sunderman, and Leopold, 1947) have determined the excretion of phenolsulphonphthalein in toxic patients and found it diminished. The impairment of renal function was found to be temporary if the treatment was discontinued soon after the appearance of symptoms (Klausner-Cronheim, 1930, Tu-Tunji, 1931, Slocumb, 1942, Debré, Thieffry, Brissaud, and Trellu, 1946, Fanelle, 1946, Covey and Whitlock, 1946). If treatment was not discontinued early, Covey and Whitlock (1946) and Debré, Thieffry, Brissaud, and Trellu (1946) found the effect on renal function to be permanent. The results in some of our patients appear to support this opinion, but few have been followed long enough for the expression 'permanent effect' to be applied (Table IV). The rise in blood-urea nitrogen has been temporary in most of our patients, falling to normal soon after the cessation of treatment.

The pathological results of intoxication with calciferol have been studied by necropsy in a small number of cases and the results are summarized in Table II. Calcification of the renal tubules was found in all patients in whom the cause of death was thought to be calciferol poisoning, and in some calcification was found elsewhere, including the myocardium in three patients. Ravina (1936) stated that calcification of myocardium, stomach wall, lungs, kidneys, intercostal muscles, thoracic aorta, and large arteries may occur. Calcification of the conjunctivae and corneae was found in a patient described by Frost, Sunderman, and Leopold (1947). Some American authors gave large doses of calciferol to patients within a month of death to observe the toxic effects and the distribution of the drug in the tissues (Spies and Hanzal, 1933, Vollmer, 1941).

There is much literature on the effects of calciferol in animals. This includes work on rats by Kreitmaier and Moll (1928), Harris and Moore (1928, 1929), Dixon and Hoyle (1928), Gough, Duguid, and Davies (1933), and Jung (1943), on mice by Kreitmaier and Moll (1928) and Schultzer and Christensen (1945), on rabbits by Smith and Elvøe (1929) and Guest and Warkany (1933), on dogs by Kreitmaier and Moll (1928), Reed and Thacker (1931), Taylor, Weld, Brannon, and Kay (1931), Steck, Deutsch, Reed, and Struck (1937), Goormaghtigh and Handovsky (1938), Brull and Clémens (1945), Hendricks, Morgan, and Freytag (1947) and Morgan, Axelrod, and Groody (1947), and on monkeys by Cowdry and Scott (1936). These investigations showed tubular (and sometimes glomerular) degeneration in the kidneys and often calcification here and

elsewhere. Dixon and Hoyle (1928) did not confirm these findings in rats. The cause of the pathological changes found is unknown, but may be some toxic product present in the circulation. This may be the calcium steroid complex responsible for the rise in diffusible serum-calcium (p. 216). The conclusions to be drawn from calcium-balance experiments conducted in patients before, during, and after treatment with calciferol will form the subject of a further communication. From the results so far obtained, it is clear that the calcium excreted is greater than that ingested during, and for a period after, calciferol therapy. Excretion of phosphorus in the urine is increased during calciferol therapy, but returns to normal on cessation of treatment. The faecal phosphorus, like the calcium, is increased during and for a period after calciferol therapy. Calciferol therefore mobilizes calcium and in large doses acts as a decalcifying agent.

Summary

1 A series of 200 patients treated with large doses of calciferol has been investigated, and the literature concerning the toxic effects of calciferol reviewed. Of these 200 patients, 38 (19 per cent.) developed toxic symptoms. There were no deaths.

2 The symptoms, signs, electrocardiographic, radiological, and biochemical findings during treatment with calciferol are described and discussed. The last include the results of estimation of the total, diffusible, and ionic calcium, the blood-urea nitrogen, serum inorganic phosphorus, serum-protein, and alkaline phosphatase. Renal function has also been investigated.

3 It is shown that calciferol given in a daily dosage of 100,000 to 150,000 i.u., or in a dosage of more than 1,100 i.u. per kg. of body-weight, may cause toxic symptoms or biochemical changes indicative of toxicity.

4 The diagnosis of toxicity may be made by consideration of the symptoms and biochemical changes, of which a rise in the diffusible serum-calcium is the most reliable. A rise above 7.5 mg. per 100 c.c. of serum-calcium appears to indicate the presence of toxicity.

5 The effects of calciferol intoxication fall most heavily on the kidneys. Impairment of function may be temporary or may persist and may be present without symptoms of toxicity.

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FACTORS INFLUENCING PLASMA CONCENTRATIONS OF SALICYLATE¹

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STRICKER (1876) was the first to recognize the value of sodium salicylate in the treatment of rheumatic fever, since when the drug has been widely studied. It was suggested by Coburn (1943) that plasma concentrations which had been attained by previous workers were below the therapeutic concentration necessary to maintain adequate control of rheumatic fever. He recommended that a plasma level of 35 mg per 100 c.c. of salicylate should be reached early and maintained. This is in keeping with other modern work which shows, as in the case of the sulphonamides, that an optimum blood level should be achieved early and then maintained. It is essential if these conditions are to be fulfilled that factors under the control of the clinician which influence plasma concentrations of salicylate should be known, and it is with such factors that the present paper is concerned. The publication of a simple but accurate method of estimating plasma salicylate by Brodie, Udenfriend, and Coburn (1944) has facilitated these studies.

The common route used for the administration of sodium salicylate is the oral one as the drug is readily absorbed from the upper gastro-intestinal tract (Hanzlik, 1926). Oral administration varying between one-hourly and four-hourly has been recommended by Morris and Graham (1931), Findlay (1931), Goodman and Gilman (1941), and Coburn (1943). Smith, Gleason, Stoll, and Ogorzalek (1946) showed that after administration of single 2 gm doses of sodium salicylate to normal adults, peak plasma concentrations were obtained two hours after oral administration, and the plasma levels fell slowly thereafter over the next six hours studied. Morris and Graham (1931) stated that when alkali was combined with salicylate, toxic symptoms were less frequent even though more salicylic ion was circulating in the blood. They considered that the addition of alkali increased the salicylate content of the blood two to four times. More recently Smull, Wégria, and Leland (1944) have found that sodium bicarbonate given in conjunction with sodium salicylate orally produces lower serum levels of salicylate than sodium salicylate administered alone, as did Smith, Gleason, Stoll, and Ogorzalek (1946). This was not confirmed by Huntington, Ryan, Butt, Griffith, Montgomery, Solley, and Leake (1946) who found that patients on 60 gr per diem of sodium salicylate showed no lower levels with the addition of bicarbonate admitting, however, that their observation period was short. Jager and Alway (1946) claimed that higher doses of

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Carnot and Blamoutier, 1925) had all used this route, but Hanzlik (1926), reviewing all the reasons given in its favour, found the therapeutic claims 'unsupported by a single iota of evidence' Since Coburn's (1943) work, many others have criticized intravenous administration, mainly on the grounds that therapeutic efficiency was not improved, among them Warren, Higley, and Coombs (1946), Wégria and Smull (1945 *a, b*), and Taran and Jacobs (1945) Jager and Alway (1946), however, were in favour of using intravenous salicylate. Manchester (1946) stated that within 48 hours salicylate levels in the plasma with oral therapy often exceeded those with intravenous therapy, except during and immediately after an intravenous injection, which had been noted by Wégria and Smull (1945 *b*) These observations require confirmation, as they appear to invalidate the primary reason for using intravenous therapy

When Smull, Wégria, and Leland (1944) showed that lower plasma concentrations were obtained when sodium bicarbonate was given with sodium salicylate, they suggested among other reasons that renal excretion might be the controlling factor Morris and Graham (1931) had found that the addition of bicarbonate increased the excretion of salicylate in the urine, but at the same time that the blood salicylate increased from two to four times The most comprehensive study of the metabolism of salicylate is the work of Kapp and Coburn (1942), who showed that salicylates were excreted in the urine partly as free salicylate, partly as salicyluric acid, and partly as the glucuronates of salicylic acid From this work Smith, Gleason, Stoll, and Ogorzalek (1946) developed a method whereby these fractions and the total salicylate content of the urine could be accurately measured They studied the excretion of salicylate over 12-hour periods and were able to show that the amount of the free salicylate fraction excreted when sodium bicarbonate was administered with sodium salicylate was appreciably greater than when sodium salicylate was given alone However, they stated that the total amount of salicylate excreted was not appreciably greater when sodium salicylate was given with bicarbonate They were able to relate the renal clearance of salicylate to the pH of the urine, which agreed with the statement of Caravati and Cosgrove (1946) that plasma concentrations of salicylate depended upon the pH of the urine

Dry, Butt, and Scheiffley (1946), using large doses of para-aminobenzoic acid with sodium salicylate orally, found that the total excretion of salicylate in the urine was diminished

The Present Investigation

The scope of the present work was to determine the influence of dosage, frequency of administration, route of administration, fluid intake, and precipitation and deterioration of mixtures of sodium salicylate and sodium bicarbonate on plasma concentrations of salicylate Excretion was studied in detail over many days, as previous workers had reached their conclusions on comparatively short periods of observation It was considered essential to correlate excretion studies with plasma salicylate concentrations and with the concurrent administration of alkaline salts, ammonium chloride, and para-aminobenzoic

sodium salicylate were required in adults and children when sodium bicarbonate was added, in order to maintain a therapeutic level at 35 mg per 100 cc Lester, Lolli, and Greenberg (1946), using acetylsalicylic acid, found that with the addition of alkali the same maximum concentration in the plasma was reached, but much earlier, a fact which led them to the conclusion that bicarbonate increased the rate of absorption of the drug. The effect of an acidifying salt, namely ammonium chloride, on the metabolism of salicylates has been noted by Smith, Gleason, Stoll, and Ogorzalek (1946). Over a period of 48 hours in convalescent patients they were able to show that an acidifying salt administered concurrently with sodium salicylate produced higher plasma levels than when sodium salicylate was given alone or with bicarbonate. This was confirmed by Caravati and Cosgrove (1946).

Using para-aminobenzoic acid empirically in the treatment of rheumatic fever Dry, Butt, and Scheisley (1946) found that its concurrent administration with sodium salicylate and bicarbonate raised the plasma level of salicylate. Thus they considered of importance as para-aminobenzoic acid might be of value in maintaining high plasma concentrations of salicylate.

The effect of varied fluid intake on plasma salicylate concentration has apparently not been studied previously. It is evident that fluid intake might be diminished during salicylate intoxication, specially in the presence of nausea and vomiting. Low fluid intake together with dehydration is described as a feature of salicylate toxicity in children by Erganian, Forbes, and Case (1947).

Variation in plasma levels may result from inaccurate dosage through precipitation and deterioration of mixtures of sodium salicylate and sodium bicarbonate in water. Deterioration of such mixtures is discussed by Hanzlik (1926), but such an effect and that of precipitation on dosage has been assessed only by Maggioni (1947), who found a diminution in salicylate content of 13 per cent after storage for one month, and when there was insufficient shaking of the bottle in the ward, a loss of up to 25 per cent of the dose occurred.

In an attempt to reduce the gastric disturbances which are well known with oral administration of sodium salicylate Heyn (1912) used the rectal route and found that maximum absorption occurred during the first 12 hours after administration. Irving (1923) had similar experiences with children, while Blume and Nohara (1933) found a higher blood concentration in rabbits after rectal administration than with the oral route. However, Mackenzie (1943) found in children that absorption was similar by both routes. Huntingdon, Ryan, Butt, Griffith, Montgomery, Solley, and Leake (1946), using 50 gr of sodium salicylate in 1 oz of water per rectum at four-hourly intervals, were unable to obtain a serum salicylate level above 7 mg per 100 cc, and decided that absorption from the rectum was poor, whereas Maggioni (1947) stated that over 50 per cent of sodium salicylate given per rectum is absorbed.

Coburn (1943) reintroduced intravenous treatment with sodium salicylate, giving as a reason that this technique produced and maintained plasma levels above 35 mg per 100 cc more quickly than oral administration. Earlier workers (Mendel, 1905, da Matta, 1910, Gilbert, Coury, and Bénard, 1921,

was repeated with the difference that 20 gr of sodium salicylate with 20 gr of sodium bicarbonate were administered every four hours. The average plasma levels for the group are shown in Table II. There was no significant difference in the levels, showing that although maximal plasma levels occur two hours after a single dose of sodium salicylate, administration every four hours was effective in maintaining plasma concentrations, probably because the fall

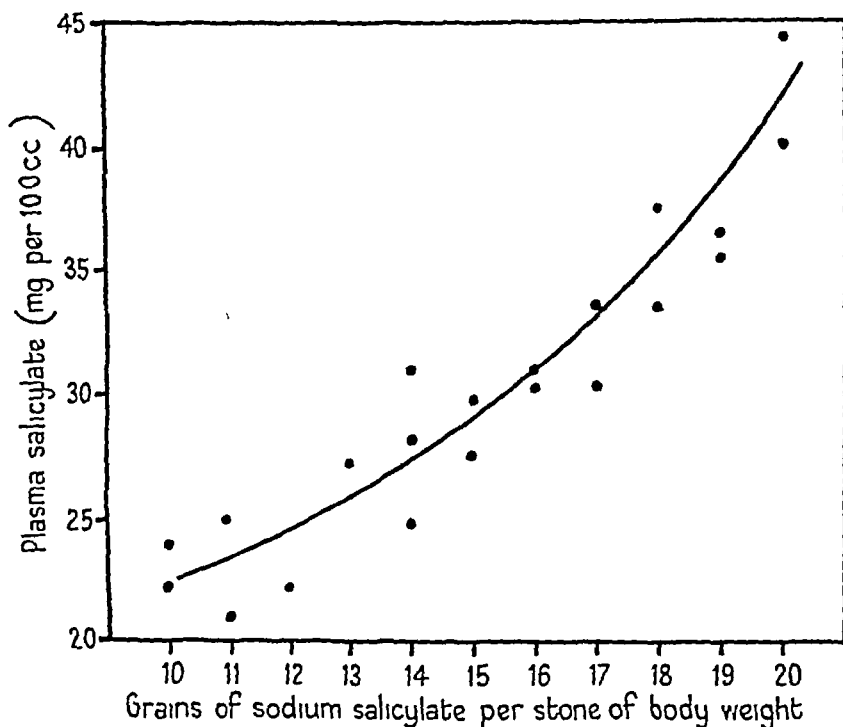


Fig 1 Plasma salicylate concentration related to dosage of sodium salicylate and body weight in adults

between the second and fourth hour after administration was relatively small.

It was difficult to assess clinically the dose of sodium salicylate which would be required to produce a given plasma level in the individual patient, so an attempt was made to correlate dose with body-weight. Twenty-one patients between the ages of 17 and 58 years were given sodium salicylate alone every four hours by mouth. In order that the plasma levels should approximate to the maximum the last three daily plasma concentrations of the first week of treatment were assessed and the average figures used in Fig 1. There was some variation in the plasma levels in patients receiving the same dose per stone of body-weight daily, but there was a general trend in the group. As the dose of sodium salicylate was increased, the rise in plasma salicylate concentration was proportionately greater. As these patients were adults it should be noted that Goodman and Gilman (1941) stated that children required larger doses than those calculated from age and weight, and Taran and Jacobs (1945) stated

noid, so that the effects of these salts on plasma concentration and excretion could be assessed in the same patients. No attempt was made to assess the specificity or efficiency of sodium salicylate in rheumatic fever. The majority of patients on whom observations were made were receiving sodium salicylate during the treatment of rheumatic fever and rheumatoid arthritis, and the remainder were convalescent.

Frequency of administration and dosage The rise and fall of plasma concentrations after various single doses of sodium salicylate by mouth were

TABLE I

The average Plasma Salicylate Concentrations (mg per 100 c c) after oral administration of single doses of Sodium Salicylate to groups of four patients

Group	I	II	III	III A
	10 gr sodium salicylate	15 gr sodium salicylate	100 gr sodium salicylate	100 gr sodium salicylate and 200 gr sodium bicarbonate
15 min			16.3	8.9
30 min			21.1	18.6
1 hr	3.5	4.2	18.1	25.6
2 hrs	4.2	9.3	31.7	28.9
3 hrs	2.6	6.4	30.1	27.1
4 hrs	2.0	5.2	28.3	21.7
8 hrs	0.3	2.4	18.1	9.2

TABLE II

Comparison of average Plasma Salicylate Concentrations (mg per 100 c c) after two-hourly and four-hourly oral administration of Sodium Salicylate to a group of four patients

Day	1	2	3	4	5	6	7
10 gr every 2 hrs	28.4	25.7	24.1	24.8	23.4	27.0	25.2
20 gr every 4 hrs	15.8	29.9	21.8	23.7	22.7	25.8	26.0

studied in three groups of patients, each group consisting of four convalescent adults. Each patient was given the dose of sodium salicylate dissolved in 2 oz of water, two and a half hours after the last meal. Venous blood was obtained and the plasma salicylate content estimated by the method of Brodie, Udenfriend, and Coburn (1944) at the times indicated in Table I, where the average plasma levels for each group are shown. The maximum plasma levels occurred two hours after administration. This did not necessarily indicate that two-hourly administration would be more successful in maintaining plasma concentration than four-hourly doses. To compare two-hourly with four-hourly administration, four adults were selected who had no detectable gastric or renal upset. They were given 10 gr of sodium salicylate with 10 gr of sodium bicarbonate at two-hourly intervals night and day for one week. Plasma levels were estimated immediately before the mid-day dose each day. Four days later, when all salicylate had disappeared from the plasma, the experiment

level, which settled within a few days (days 10 to 14). When the fluid intake was restricted to 50 oz. there was a marked rise in plasma concentration after several days. Resumption of a copious fluid intake after a period of restriction led to a speedy lowering of plasma concentration. In a further two patients the use of a mercurial diuretic (mersalyl) in the presence of a low fluid intake further increased the plasma concentration of salicylate, but in the presence of an adequate fluid intake the mercurial diuretic produced no measurable effect on the plasma levels, although diuresis was greater. This indicated that the diuretic produced its effect on plasma levels of salicylate by aggravating the fluid depletion of the body rather than by influencing renal excretion of the salicylate. It appeared then that as the body fluid decreased, plasma salicylate increased if oral dosage of sodium salicylate was maintained, but that this effect occurred only when there was some dehydration present (after several days of low fluid intake). The rise in plasma salicylate under such conditions was marked. These results have been demonstrated in adults, but it is likely that in children, in whom dehydration is an early feature of salicylate toxicity (Ergaman, Forbes, and Case, 1947), such toxicity may be greatly aggravated by lack of fluid. It is apparent also that the administration of adequate amounts of fluid will do much to relieve the symptoms of severe salicylate poisoning.

Inaccurate dosage and deterioration of mixtures. In our hospital the standard method of dispensing sodium salicylate was in a mixture containing sodium bicarbonate, the combined dose of both ingredients being carried in $\frac{1}{2}$ oz. of water. Several bottles containing 12 oz. of a mixture of 30 gr. of sodium salicylate and 30 gr. of sodium bicarbonate in $\frac{1}{2}$ oz. of water which had been accurately dispensed were selected and the contents measured into single $\frac{1}{2}$ -oz. doses, but only after the usual amount of shaking done by the ward nurse. All sediment was allowed to settle and the bottle shaken again before each measurement. The doses were then suitably diluted and the salicylate content determined. It was found that the initial 12 doses from each bottle contained 95 to 120 per cent. of the correct amount, while the last 12 doses contained 70 to 100 per cent. This indicated that inadequate shaking gave an error, probably from the uneven distribution of the undissolved bicarbonate. Moreover, towards the bottom of a bottle the patient received greater amounts of bicarbonate than at the start, which as is shown below has an effect on the excretion of salicylate. After standing on a laboratory shelf for three weeks in daylight, mixtures yielded to 10 per cent. less salicylate as estimated before and after this period of time. To ensure accuracy, solutions of sodium salicylate should be freshly prepared and the sodium bicarbonate dispensed separately.

Rectal administration. The majority of workers have compared the rectal and oral route by examination of excretion of salicylate or by therapeutic and toxic manifestations, methods which give only indirect and not necessarily accurate pictures of absorption and concentration in the circulation. In the following investigations, after a voiding enema had been returned, the sodium salicylate was dissolved in 3 oz. of water and run into the rectum. The tubing and

that $1\frac{1}{2}$ gr per pound of body-weight daily would be required to raise the plasma salicylate concentration in children to 35 to 40 mg per 100 cc

The addition of sodium bicarbonate to sodium salicylate The effect of the addition of sodium bicarbonate to single doses of sodium salicylate was assessed in the group of patients on whom plasma levels resultant on a single dose of 100 gr of sodium salicylate alone had been obtained previously In this instance

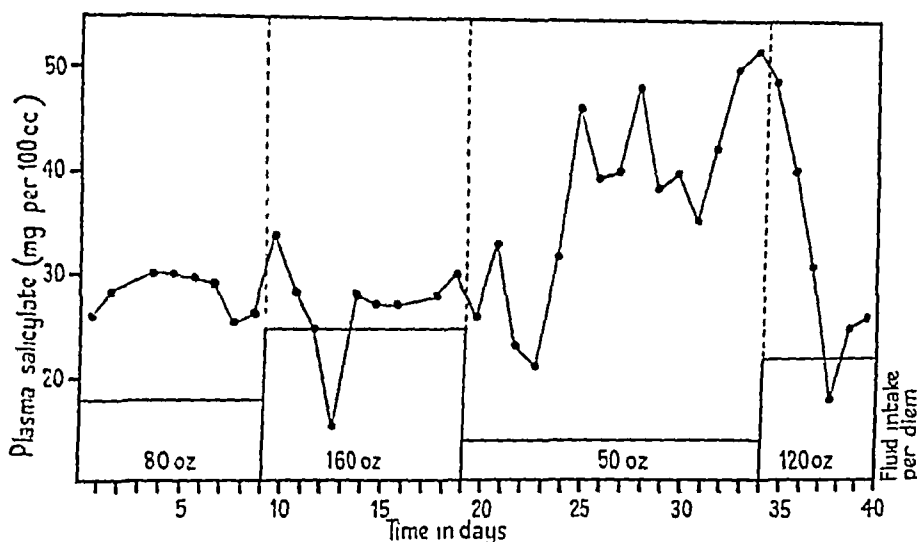


Fig. 2 The relationship between fluid intake and plasma salicylate concentration when a fixed daily amount of sodium salicylate is given The subject was a man aged 42 years, weighing 8 stone, with chronic rheumatoid arthritis, he received 20 gr each of sodium salicylate and sodium bicarbonate four hourly

under similar conditions these patients were given 100 gr of sodium salicylate with 200 gr of sodium bicarbonate The average plasma salicylate levels obtained are shown in Table I With and without bicarbonate the maximum concentrations obtained were comparable After the maximal concentrations were reached the concentration fell away more rapidly with the concurrent alkali administration Thus the addition of alkali did not affect the absorption of sodium salicylate from the upper gastro-intestinal tract, but facilitated its elimination from the circulation This latter phenomenon is studied further below

Fluid intake To assess the effect of fluid intake on plasma concentrations of the drug, four adults were given 20 gr of sodium salicylate and 20 gr of sodium bicarbonate every four hours for 40 days The fluid intake was varied from 50 to 160 oz daily over periods of several days Daily plasma concentrations showed similar fluctuations in all four patients The results in one patient, a man aged 42 years who was suffering from chronic rheumatoid arthritis, are shown as being representative in Fig 2 There was little effect on plasma concentration while the fluid intake remained above 50 oz per diem Variation in the fluid intake above this amount produced a temporary upset in the plasma

Case 1 A man 26 years of age was admitted with a flitting arthritis, involving knees, ankles, wrists, and shoulders which had been present for three weeks. The temperature was 100° F, pulse 94, and blood-pressure 120/60. There was cardiac enlargement, arrhythmia, or bruits. The haemoglobin was 13.4 gm per 100 c.c., erythrocyte sedimentation rate 94 mm in first hour, 105 mm in second hour, white cells 8,000 per c.mm. and red cells 4,500,000 per c.mm. Radiological evidence of bone abnormality was detected. Rectal sodium salicylate administration was commenced with the dose of 60 gr in 3 oz of water every eight hours.

Plasma levels		
Day	(mg per 100 c.c.)	
2	13.6	Less arthralgia. Temperature normal. Tinnitus present.
3	14.3	No joint pains. Tinnitus and slight deafness. Pulse-rate 72.
4	26.6	Persistent tinnitus and deafness. Erythrocyte sedimentation rate 65 mm in first hour, 86 mm in second hour.
5	23.6	Deeper respiration, some sweating but comfortable.
6	32.1	Sodium bicarbonate gr 60 orally, thrice daily, after attack of nausea.
7	28.0	Respiration normal, no nausea. Sodium bicarbonate discontinued.
15	28.2	
26	28.0	
28		Salicylate discontinued.
30		No further symptoms. Allowed up slowly. Haemoglobin 14.5 gm per 100 c.c. Erythrocyte sedimentation rate 3 mm in first hour, 12 mm in second hour, white cells 9,000 per c.mm., red cells 4,760,000 per c.mm. Blood-pressure 125/75.
39		Discharged.

Reviewed one month later—no abnormality or complaint.

The patient showed remarkably steady levels on rectal salicylate. He had an uneventful recovery with all clinical signs disappearing by the fourth day of treatment, except for a raised erythrocyte sedimentation rate. The patient had no difficulty with defaecation, passing a daily motion before the morning enema and an occasional small soft stool during the afternoon. There was no rectal irritation or difficulty in retaining the salicylate enema.

Case 2 A boy aged 12 years was admitted with flitting arthritis involving the ankles, wrists, knees, and elbows, of 12 days' duration. There had been a sore throat three weeks previously. There was no previous history of rheumatism. The temperature was 101° F, pulse-rate 140, and respiration 24. The white cells were 10,000 per c.mm., haemoglobin 13 gm per 100 c.c., red cells 4,000,000 per c.mm., erythrocyte sedimentation rate 86 mm in first hour, 102 mm in second hour. Moderate cardiac enlargement with an apical systolic conducted bruit. No diastolic murmur. Electrocardiogram, PR interval 0.25 sec. Rectal sodium salicylate was administered, 40 gr in 2 oz water in eight-hourly enemata.

Plasma levels		
Day	(mg per 100 c.c.)	
2	22.6	Erythrocyte sedimentation rate 80 mm in first hour. Joint pains less severe. Pulse rate 140.
3	36.5	Tinnitus, deafness, and sweating. No joint pains. Pulse rate 120.
4	42.1	Tinnitus, deafness, and slight nausea. Normal temperature. Pulse rate 120.
5	39.8	
9	42.0	Erythrocyte sedimentation rate 88 mm in first hour. Pulse rate 110. Tinnitus and deafness only.
13	35.6	

catheter were then washed through with one more ounce of water. All fluids were at body temperature. Five patients were given 100 gr of sodium salicylate in 4 oz of water orally two and a half hours after the last meal, and plasma concentrations obtained at the times indicated in Fig 3. Several days later, when all salicylate had been excreted, the same dose was given, but this time per rectum. The average plasma levels for the group are compared with those

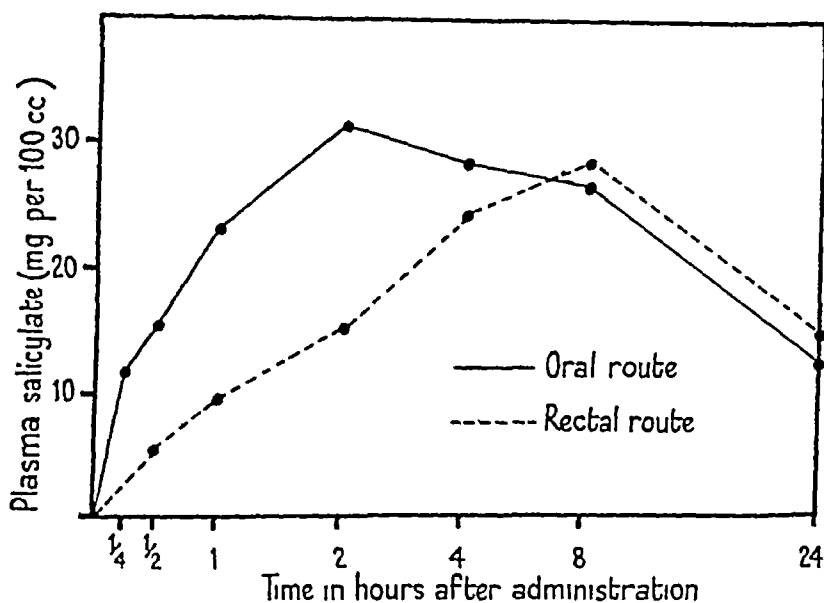


FIG 3 The average plasma levels in a group of five patients after oral and then rectal administration of 100 gr of sodium salicylate

obtained by oral administration in Fig 3. The maximal plasma concentrations after rectal administration were delayed, occurring eight hours after enemata were given. This showed that absorption from the rectal mucosa was slower than from the upper gastro-intestinal tract. The maximum concentrations obtained by the oral route were slightly higher than those obtained when the drug was given per rectum, probably because there was a longer period before plasma concentration reached a maximum, during which excretion was taking place. The rate of elimination of salicylate from the plasma after the maximal concentrations by both routes had been attained was comparable. When sodium bicarbonate was added in equal quantities to the sodium salicylate in the enemata, it was found that peak plasma concentrations occurred from 10 to 14 hours after administration, and that these levels were lower than those obtained with the same dose of sodium salicylate alone. There appeared to be slower absorption of sodium salicylate from the rectum in the presence of alkali. Having established that maximal plasma levels occurred eight hours after rectal administration, two patients with acute rheumatic fever were treated by the rectal route with sodium salicylate.

matic carditis was evident. Where vomiting or nausea precluded the oral administration of sodium salicylate, the rectal route was found to be a preferable choice to the intravenous one. Because of the reasons mentioned above, we have abandoned the intravenous route.

The excretion of sodium salicylate. The only references to excretion of salicylate in the faeces and sweat, which are the other possible routes of salicylate

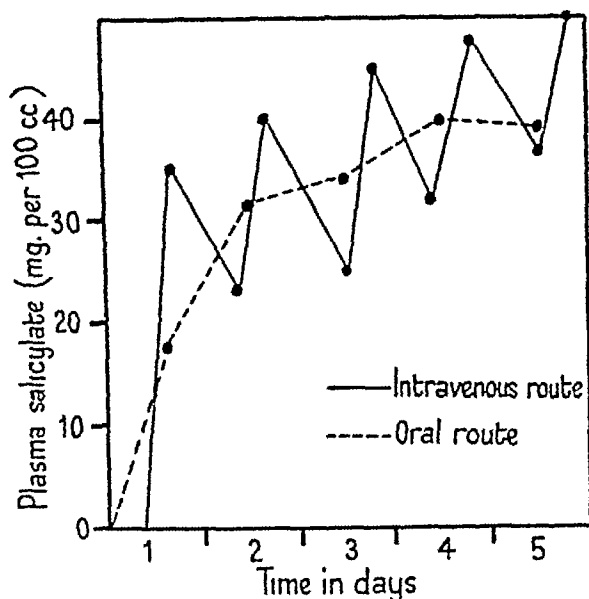


FIG. 4 Comparison of plasma salicylate concentrations obtained by intravenous and oral administration of 10 gm of sodium salicylate daily.

elimination from the body, were that of Hanzlik (1926), who considered that only negligible quantities were lost in the faeces and sweat, and that of Morris and Graham (1931), who found no salicylate in one specimen of faeces from a patient undergoing salicylate therapy. Before any assessment of urinary excretion was made it was necessary to confirm that the other possible routes were of no importance. Sweat was obtained with a clean, dry sponge from patients undergoing salicylate therapy for rheumatic fever. Pilocarpine nitrate gr 1/5 was injected subcutaneously when perspiration was insufficient to allow collection of 1 c c by this means. The salicylate concentration was estimated in the samples obtained by the method described for plasma by Brodie, Udenfriend, and Coburn (1944). No trace of salicylate was detected in these samples. Sixteen samples of faeces were examined from patients receiving salicylate in various doses by mouth. Three consecutive daily specimens were examined from four patients receiving 12 gm of sodium salicylate daily and four consecutive samples from a patient receiving 24 gm of sodium salicylate daily. The last patient had been receiving sodium salicylate over a period of three months and was showing only moderate plasma concentrations in spite of

<i>Plasma levels</i>		
<i>Day</i>	<i>(mg per 100 c c)</i>	
16	42.5	Slight nausea
21	36.4	Erythrocyte sedimentation rate 42 mm in first hour No nausea Tinnitus and deafness persisted throughout from this time
23	38.2	
31	30.6	Erythrocyte sedimentation rate 28 mm in first hour Pulse rate 90
35	32.6	
40	30.8	Erythrocyte sedimentation rate 15 mm in first hour Pulse rate 78 Electrocardiogram, PR interval 0.18 sec
46	28.6	Erythrocyte sedimentation rate 8 mm in first hour Pulse rate 82
53	20.6	Erythrocyte sedimentation rate 5 mm in first hour Pulse rate 82
60	26.6	Erythrocyte sedimentation rate 5 mm in first hour Pulse rate 78
61		Rectal salicylate discontinued
63		No further symptoms Allowed up slowly
74		Haemoglobin 14 gm per 100 c c, white cells 9,000 per c.mm., red cells 4,500,000 per c mm Erythrocyte sedimentation rate 4 mm in first hour, 12 mm in second hour No cardiac enlargement, but a conducted bruit systolic in time Discharged

Reviewed three weeks later—no further symptoms

This case also showed an uneventful recovery. The plasma levels were well maintained, and only minor toxic manifestations were seen.

Thus both patients showed remarkably steady levels throughout treatment, with clinical improvement within 48 hours, and both appeared well on discharge and after a short follow-up period. There was minimal upset in bowel rhythm and no rectal symptoms during treatment.

Intravenous administration. Plasma concentrations from intravenous and oral therapy were compared. Five male adults were given 10 gm of sodium salicylate in 1,000 c c of normal saline intravenously over eight-hour periods daily for five days. Some days later, when all salicylate had been excreted, the patients were given 10 gm of sodium salicylate orally in four-hourly divided doses for five days. With intravenous therapy plasma salicylate levels were estimated daily before and after each injection, and with oral administration daily immediately before the mid-day dose. The plasma concentrations of salicylate obtained are shown as average plasma levels for the group of patients in Fig. 4. High peaks occurred immediately after intravenous injection, but fell considerably by the next morning. The plasma levels with oral therapy were steady, and compared favourably with those obtained by the intravenous route, apart from the period immediately after an intravenous injection. Random plasma estimations taken after intravenous injection showed that the fall in concentration was rapid immediately after the injection, which indicated that the highest intravenous levels were of short duration. The technique of intravenous injection was more difficult than that of oral dosage and was resented by patients because eight-hour immobilization of a limb was uncomfortable. Moreover, the danger of overloading the circulation in the presence of rheu-

matic carditis was evident. Where vomiting or nausea precluded the oral administration of sodium salicylate, the rectal route was found to be a preferable choice to the intravenous one. Because of the reasons mentioned above, we have abandoned the intravenous route.

The excretion of sodium salicylate The only references to excretion of salicylate in the faeces and sweat, which are the other possible routes of salicylate

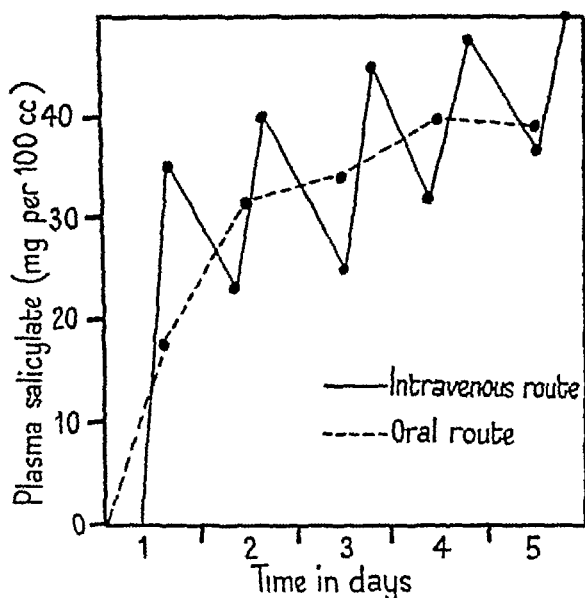


FIG. 4. Comparison of plasma salicylate concentrations obtained by intravenous and oral administration of 10 gm of sodium salicylate daily.

elimination from the body, were that of Hanzlik (1926), who considered that only negligible quantities were lost in the faeces and sweat, and that of Morris and Graham (1931), who found no salicylate in one specimen of faeces from a patient undergoing salicylate therapy. Before any assessment of urinary excretion was made it was necessary to confirm that the other possible routes were of no importance. Sweat was obtained with a clean, dry sponge from patients undergoing salicylate therapy for rheumatic fever. Pilocarpine nitrate gr 1/5 was injected subcutaneously when perspiration was insufficient to allow collection of 1 cc by this means. The salicylate concentration was estimated in the samples obtained by the method described for plasma by Brodie, Udenfriend, and Coburn (1944). No trace of salicylate was detected in these samples. Sixteen samples of faeces were examined from patients receiving salicylate in various doses by mouth. Three consecutive daily specimens were examined from four patients receiving 12 gm. of sodium salicylate daily and four consecutive samples from a patient receiving 24 gm. of sodium salicylate daily. The last patient had been receiving sodium salicylate over a period of three months and was showing only moderate plasma concentrations in spite of

gradually increasing dosage, a feature observed in many patients in whom salicylate therapy was prolonged. Five gm of the stool under examination were emulsified in 10 c.c. of distilled water and placed in a conical flask in which 10 c.c. of concentrated hydrochloric acid had been placed. The contents were hydrolysed by boiling for four hours, the flask being attached to a reflux condenser to prevent loss of salicylate. The total salicylate was then estimated

TABLE III

The Effect in a Man of 42 Years of Concurrent Oral Administration of Sodium Bicarbonate and Ammonium Chloride with Sodium Salicylate on the Total Excretion of Salicylate in the Urine, and on Plasma Salicylate Concentrations

Daily dosage	Day	Plasma level (mg per 100 c.c.)	Amount of urine in 24 hrs (c.c.)	Total sali- cylate excreted (gm.)
Sodium sali- cylate 6 gm. alone	1	21.2	1,120	2.85
	2	24.2	1,010	3.25
	3	28.1	1,025	2.88
	4	24.2	1,225	2.75
	5	20.1	1,025	2.92
	Average for period		1,081	2.93
Sodium sali- cylate 6 gm + sodium bicarbonate 6 gm	6	19.4	1,083	3.35
	7	23.6	1,140	3.42
	8	23.8	1,254	3.64
	9	20.2	1,250	3.33
	10	19.2	855	3.21
	Average for period		1,116	3.39
Sodium sali- cylate 6 gm + ammonium chloride 6 gm	11	26.6	1,425	3.08
	12	29.2	1,140	2.57
	13	29.2	1,083	2.50
	14	27.6	1,197	2.75
	15	23.5	1,140	2.92
	Average for period		1,197	2.76

in the filtrate by the method described for plasma by Brodie, Udenfriend, and Coburn (1944), after blanks and normal stools to which known quantities had been added had shown the method to be accurate. Only four of the 16 stools examined yielded a trace of salicylate, which when related to the total weight of faeces passed in the 24 hours varied from 0.2 to 0.4 gm of sodium salicylate.

Urinary excretion of salicylate was studied in numerous patients. Each patient was given sodium salicylate for four or more days until plasma concentrations were steady before observations were made. Each day, plasma concentration of salicylate was estimated at mid-day. Twenty-four-hour specimens of urine were collected, measured, and their total content of salicylate, with separate estimation of the individual salicyl fractions, determined by the method of Smith, Gleason, Stoll, and Ogorzalek (1946). This was done after the pH of the specimens had been determined by indicators. Doses of sodium salicylate alone and sodium salicylate concurrently with alkaline salts, ammonium chloride, and para-aminobenzoic acid were administered orally at four-hourly intervals night and day. All relevant information and results from four

of the many patients studied are shown in Tables III to VI. These illustrate the findings which occurred in all patients. Tables III and IV showed that the concurrent administration of sodium bicarbonate produced a marked rise in the total salicylate excretion, in contradistinction to the findings of Smith, Gleason, Stoll, and Ogorzalek (1946) who, however, stopped their short-period urinary estimations while an appreciable concentration of salicylate remained in the

TABLE IV

The Effect in a Man of 32 Years of Concurrent Oral Administration of Alkaline and Acid Salts on Plasma Concentration of Salicylate, and on the Excretion of the Salicyl Fractions in the Urine.

Daily dosage	Day	Plasma level (mg per 100 c c)	Amount of urine (c c)	24-hour excretion			
				Salicyluric acid (gm)	Free salicylate (gm)	Salicyl glyconates (gm)	Total salicylate (gm)
Sodium salicylate 12 gm +sodium bicarbonate 12 gm	1	20.2	1,860	2.78	3.86	1.49	8.13
	2	18.2	1,900	2.96	4.89	1.53	9.38
	3	16.4	1,770	2.67	3.31	1.37	7.35
	Average for period		1,843	2.80	4.02	1.48	8.28
Sodium salicylate 12 gm alone	4	17.5	1,150	1.29	1.06	1.44	3.79
	5	22.9	1,105	2.42	3.65	0.99	6.96
	6	23.6	1,250	1.87	2.03	1.12	5.02
	7	24.1	1,360	1.98	1.50	1.82	5.30
	8	22.8	2,260	2.30	1.51	1.39	5.20
	Average for period		1,425	1.99	1.95	1.35	5.25
Sodium salicylate 12 gm +ammonium chloride 6 gm	9	21.6	1,900	1.02	0.96	1.70	3.69
	10	33.0	1,740	1.46	1.65	1.35	4.46
	11	33.2	2,280	1.45	1.66	2.16	5.27
	12	31.8	1,870	1.68	1.54	2.34	5.56
	Average for period		1,558	1.40	1.45	1.89	4.72

plasma. The excretion of total salicylate was lowest when ammonium chloride (an acidifying salt) was administered with sodium salicylate, but not much lower than when sodium salicylate was given alone by mouth. It will be seen from the 24-hour volumes of urine obtained that the varying quantities passed played no part in altering the daily excretion of salicylate.

Tables III, IV, and V show that in all patients receiving sodium salicylate alone the recovery of the drug from the urine varied from 44 to 49 per cent of the total dose, irrespective of the amount administered, while when alkali was given concurrently 56 to 79 per cent was recovered. Under optimum conditions of recovery over 20 per cent of salicylate disappeared. The mechanism is unknown, but deterioration of sodium salicylate *in vitro* is known to occur. It seemed unlikely that the concurrent administration of alkali increased the amount of salicylate excreted in the urine by decreasing this destruction of salicylate, because the plasma salicylate fell on each occasion when excretion increased. The fraction in the urine which shows the greatest variation in excretion is the free salicylate. Here the greatest excretion follows

the administration of an alkaline salt, while the lowest excretion occurs with concurrent administration of an acidifying salt. This is the fraction which pro-

TABLE V

The Effect in a Youth of 19 Years of Concurrent Oral Administration of Potassium Citrate and Ammonium Chloride on the Plasma Concentration of Salicylate and on the Salicyl Excretion in the Urine

Daily dosage	Day	Plasma level (mg per 100 c c)	Amount of urine in 24 hrs (c c.)	24 hour excretion			
				Salicyluric acid (gm)	Free salicylate (gm)	Salicyl glyconates (gm)	Total salicylate (gm)
Sodium salicylate 10 gm. alone	1	18.2	1,860	1.26	0.65	1.82	3.73
	2	23.7	1,300	1.03	2.44	1.98	6.35
	3	25.6	1,160	1.11	1.49	1.84	4.44
	4	21.2	820	0.89	2.06	2.01	4.96
Average for period			1,300	1.29	1.66	1.91	4.87
Sodium salicylate 10 gm + potassium citrate 6 gm	5	22.6	1,780	2.49	6.23	1.20	9.92
	6	18.4	1,085	2.05	3.03	1.52	6.65
	7	16.6	1,000	1.46	3.63	2.28	7.37
	8	15.2	1,560	2.24	3.84	1.63	7.71
Average for period			1,820	2.06	4.19	1.65	7.91
Sodium salicylate 10 gm. + ammonium chloride 6 gm	9	17.8	1,760	1.37	1.74	2.11	5.22
	10	28.4	2,300	1.38	0.22	2.56	4.16
	11	28.4	1,840	1.30	0.33	2.47	4.13
	12	29.6	1,160	1.22	0.57	2.39	4.18
Average for period			1,770	1.31	0.71	2.38	4.42

TABLE VI

The Effect, in a Man of 21 Years, on Plasma Concentrations of Salicylate and on the Excretion of the Salicyl Fractions in the Urine of Massive Doses of Para aminobenzoic Acid when given concurrently with Sodium Salicylate and Sodium Bicarbonate

Daily dosage	Day	Plasma level (mg per 100 c c)	Amount of urine in 24 hrs (c c.)	24 hour excretion			
				Salicyluric acid (gm)	Free salicylate (gm)	Salicyl glyconates (gm)	Total salicylate (gm)
Sodium salicylate 12 gm + sodium bicarbonate 12 gm	1	19.2	2,100	3.58	2.60	0.90	7.08
	2	22.2	2,470	3.42	2.30	1.12	6.84
	3	19.0	2,610	3.59	1.82	1.20	6.61
Average for period			2,393	3.53	2.24	1.07	6.84
Sodium salicylate 12 gm + para-aminobenzoic acid 24 gm	4	31.6	2,610	4.01	0.54	1.30	6.26
	5	43.2	1,790	2.86	0.17	1.32	4.45
	6	41.4	1,510	3.02	1.19	1.33	5.54
Average for period			1,970	3.29	0.63	1.31	5.41

duces the significant difference in total excretion of salicylate when these alkaline salts and this acidifying salt are given together with sodium salicylate. That the varying excretion of this fraction is of an order which might explain

the effect of these salts on the plasma concentration of salicylate can be seen in Tables IV and V. On surveying all patients studied, including others in whom plasma concentrations were followed when alkali was added, it was found that the addition of alkali in equal quantities to the sodium salicylate given orally caused a reduction in plasma salicylate concentration on each occasion of from 10 to 35 per cent.

Table VI indicates that para-aminobenzoic acid produces an effect similar

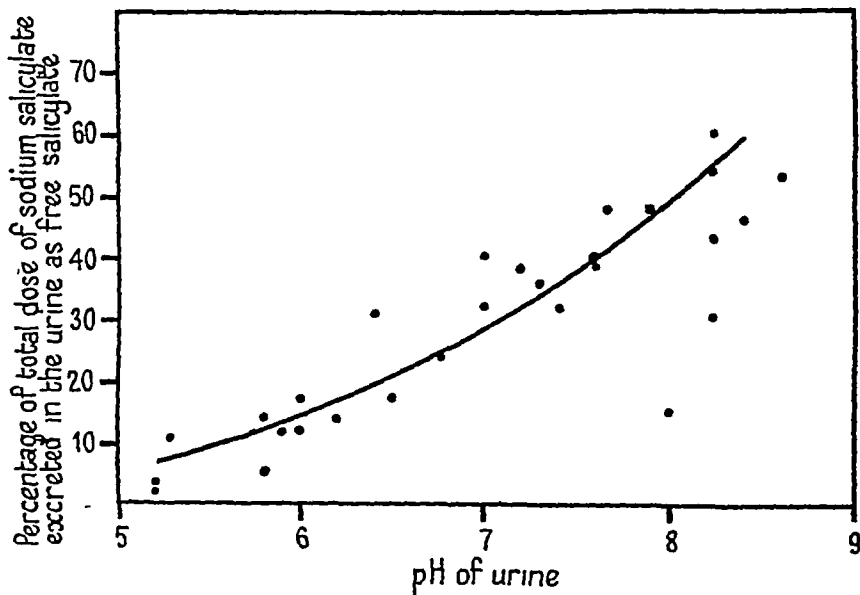


FIG 5 The relationship between the percentage of the daily dose of sodium salicylate excreted in the urine as free salicylate and the pH of the urine

to the administration of an acidifying salt, the total salicylate excretion being diminished, which is in agreement with the observation of Dry, Butt, and Schoenley (1946). This effect is brought about mainly by a decreased excretion of the free salicylate fraction in the urine. The large doses of para-aminobenzoic acid used induced no toxicity other than that due to increased plasma concentration of salicylate, but white-cell counts were performed daily during treatment as a precaution. Tierney (1946), using even larger doses of para-aminobenzoic acid in the treatment of tsutsugamushi disease, found no toxicity.

In our experiments the smallest excretion of free salicylate coincided with the lowest pH in the urine. To relate the excretion of free salicylate to pH of the urine a common factor was determined, namely, that percentage of the total daily dose which was excreted in the urine as free salicylate. The relationship of this factor to pH of the urine is demonstrated in Fig 5. As the pH of the urine rose so did the percentage of the total dose of salicylate excreted in the urine as free salicylate. The concurrent administration of alkaline salts,

ammonium chloride, and para-aminobenzoic acid appeared to exert an influence through the pH of the urine. This supports the evidence of Smith, Gleason, Stoll, and Ogorzalek (1946) that renal clearance of salicylate rises with pH of the urine and the statement of Caravati and Cosgrove (1946) that plasma levels of salicylate depend on the pH of the urine. Table V shows that potassium citrate increased the excretion of salicylate in the urine with consequent lowering of plasma salicylate concentration, indicating that alkaline salts other than sodium bicarbonate have this action. It appears that to render the urine alkaline and maintain an adequate fluid intake are essentials in the treatment of salicylate poisoning, and that knowledge of urinary pH and fluid intake will go far to explain differences in plasma concentration from day to day in patients receiving a fixed daily dose of sodium salicylate. Graham and Parker (1948) have shown that plasma concentration can be related to toxic manifestations of sodium salicylate, and as it has been shown in the present paper that alkaline salts produce a reduction in plasma concentration when given orally with sodium salicylate it follows that concurrent alkali administration will reduce the toxicity of a given dose of the drug.

Conclusions

In the presence of an adequate fluid intake it appears that adults require about 18 gr of sodium salicylate daily per stone of body-weight to produce and maintain a plasma concentration of 35 mg per 100 c c, and that this should be given in four-hourly divided doses by the mouth. If sodium bicarbonate is given concurrently in equal quantities, an increase in dosage of sodium salicylate from 1 to 2 gr per stone of body-weight will be required. The concurrent administration of ammonium chloride or para-aminobenzoic acid will cause a rise in plasma concentration.

Rectal enemas of sodium salicylate given at eight-hourly intervals will maintain satisfactory plasma concentrations and can be used in the treatment of rheumatic fever over long periods. There is no advantage to be gained by intravenous administration of sodium salicylate.

Fluid intake should be maintained above 3 pints per diem, as a lower intake over several days will cause sudden and marked increase in plasma concentration of salicylate. Fluid and alkali should be given in salicylate poisoning to facilitate excretion of the drug.

Fluctuation in pH of the urine may explain some variation in plasma levels from day to day in patients receiving a fixed dose of the drug. With prolonged administration of sodium salicylate increasing doses will be required to maintain initial plasma concentrations.

To ensure accuracy of dosage, sodium salicylate should be freshly dispensed if dissolved in water, and sodium bicarbonate if given should be dispensed separately.

Summary

1 A study of factors under the control of the clinician which influence plasma concentrations of salicylate after the administration of sodium salicylate was made in patients suffering from rheumatic fever and rheumatoid arthritis, and in convalescents

2 Although maximal plasma concentrations occurred two hours after oral administration, four-hourly dosage maintained plasma levels successfully

3 A relationship between dose and body-weight in adults was shown

4 A low fluid intake increased plasma concentration of salicylate when a fixed daily dose of sodium salicylate was continued. After such a rise the resumption of adequate fluid intake speedily diminished plasma concentrations.

5 There was a reduction of 10 per cent in salicylate content of mixtures of sodium salicylate and sodium bicarbonate after standing for three weeks. Inadequate shaking of such mixtures before administration caused the salicylate content of a dose to vary from 70 to 120 per cent of the expected amount

6 Maximal plasma concentrations followed eight hours after rectal administration of sodium salicylate, but the addition of alkali diminished absorption of the drug from the rectum. Satisfactory plasma levels and therapeutic response was shown in two cases of rheumatic fever treated by the rectal route throughout the illness

7 Plasma concentrations obtained by oral and intravenous administration of sodium salicylate were compared, and no advantage was found in the intravenous administration of sodium salicylate

8 Urinary excretion was correlated with plasma concentrations of salicylate and with concurrent administration of sodium bicarbonate, potassium citrate, ammonium chloride, and para-aminobenzoic acid, after it had been shown that no salicylate was excreted in the sweat and only negligible quantities in the faeces. It was shown that alkaline salts diminished plasma salicylate concentration by from 10 to 35 per cent by causing an increased excretion of free salicylate in the urine, while ammonium chloride and para-aminobenzoic acid had the opposite effect. A direct relationship between increased excretion of free salicylate and the pH of the urine was shown

I must record my debt to the late Professor N. Morris, in whose wards this work was carried out, for his encouragement and critical interest

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HAEMOCHROMATOSIS OBSERVATIONS ON THE INCIDENCE AND ON THE VALUE OF LIVER BIOPSY IN DIAGNOSIS¹

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With Plates 18 to 20

HAEMOCHROMATOSIS, from a survey of the literature, must be regarded as a rare disease. The purposes of the present communication are threefold, to record the incidence of haemochromatosis in the Alfred Hospital over the past 12 years, to describe seven cases of the disease, five of which were admitted to the Alfred Hospital and two to Heidelberg Military Hospital, and to suggest the value of liver biopsy in diagnosis.

Incidence of haemochromatosis in the Alfred Hospital Within the past 12 years, 13 proven cases of haemochromatosis have been admitted to the Alfred Hospital. Seven have been described by Willis (1941) in an earlier paper, five are now to be described, and one has not been reported. Ten of these 13 cases were male and three female. The diagnosis was made during life in five and at autopsy in eight. The 13 cases have occurred in the course of approximately 78,000 admissions to the hospital. This represents a considerably greater incidence in general hospital practice than has hitherto been described (Althausen and Kerr, 1933). Likewise, the proportion of female to male patients is much in excess of the figures previously published (Sheldon, 1935, Butt and Wilder, 1938, Lawrence, 1940).

Case Reports

Of the seven cases now to be described, the diagnosis was made during life in six and at autopsy in one. Two of the patients were female and five male.

Case 1 A woman, aged 54 years, was first seen at the Alfred Hospital on July 27, 1939. She complained of increasing polyuria and thirst for the previous 12 months. For about the same length of time she had been aware of an increasing brown discoloration of her skin, which had also become dry and scaly, this change had been more noticeable on the face and hands. She had also felt a sensation of weight and a lump in the right upper abdomen for 12 months. There had been marked loss of hair during the previous six months, and for three months prior to her admission she had been easily tired and lacking in energy. There had been a loss of approximately two stone in weight during this period. There was no history of dyspepsia or jaundice. The family history revealed that a maternal uncle had suffered from diabetes. There was no family

¹ Received March 11, 1948

history of pigmentation Her past history was of no significance Fifteen years before admission she had suffered from 'rheumatism', which she stated had been attributed to pyorrhoea and had yielded to treatment Apart from this, she had suffered from no illnesses since childhood She admitted to taking an occasional glass of beer

Examination at the time of admission revealed a thin, middle-aged woman with generalized slaty pigmentation which was more marked on the face and hands There had been a considerable loss of hair from the scalp, axillae, and pubic regions No abnormality was found on examination of the cardiovascular or respiratory systems The blood-pressure was 140/90 No abnormality was detected in the central nervous system Examination of the abdomen revealed a grossly enlarged liver, the edge of which was palpable at a distance of five fingers' breadths below the right costal margin The surface was somewhat irregular, suggesting the presence of cirrhotic nodules The tip of the spleen was palpable on deep inspiration No ascites or other abnormalities were detected The diagnosis of haemochromatosis was suggested by the clinical findings and was subsequently confirmed by glucose tolerance tests, skin biopsy, and other investigations, the results of which are set out in detail in the Table (pp 250-1). Her diabetic condition was controlled satisfactorily by a diet of carbohydrate 200 gm, protein 100 gm, fat 175 gm (2,775 calories), and 45 units of soluble insulin before the morning meal and 40 units of soluble insulin before the evening meal She was discharged from hospital after six weeks' treatment, and remained continuously under observation in the Out-Patient Department until September 1941 During these two years she enjoyed satisfactory health and regained her weight and strength The diabetic condition remained under control without any alteration of insulin dosage or any disturbances in tolerance In September 1941 she complained of the sudden onset of dyspnoea on exertion and a sense of suffocation at night, and she had noticed a decrease in her capacity for effort during the previous four weeks She was readmitted to hospital Examination at this time revealed some oedema of the feet and fullness of the neck veins Clinical examination of the heart disclosed no alteration in size, but the rhythm was irregular, the apical rate being 140 An electrocardiogram proved the irregularity to be due to auricular fibrillation, and some left-axis deviation was also noticed No alteration was detected in the size of the liver The blood-pressure was 130/80 The fibrillation was controlled with appropriate doses of tincture of digitalis and her diet was modified to carbohydrate 150 gm, protein 70 gm, fat 120 gm (1,960 calories), with 58 units of soluble insulin in the morning and evening She was discharged early in October with slow fibrillation, but with no signs of congestive failure She was not seen again until December 22, 1941, when she was admitted to the Royal Melbourne Hospital in an extreme state of cardiac failure She failed to respond to treatment and died on December 23, 1941 An autopsy was not performed

Case 2 A woman aged 47 years, by occupation a waitress, was first seen at the Alfred Hospital on March 16, 1946 She complained of increasing lassitude and loss of energy for the previous six months, during which period she had lost approximately two and a half stone in weight Increasing thirst and polyuria had been noticed for two months She was not aware of any change in the colour of her skin, nor was it possible on questioning to determine when this change occurred, although at the time of her admission it was obvious that she was deeply pigmented The family history revealed no evidence of diabetes mellitus or pigmentation She had suffered from no illnesses since childhood, and stated that she had been a teetotaller throughout life

Examination at the time of admission revealed a thin woman with no obvious loss of hair. The skin of her trunk and limbs was dry and of a characteristic brownish hue, thus being more marked on the face, forearms, and hands than elsewhere. There was some pigmentation of the buccal mucosa. Clinical examination of the cardiovascular system and respiratory system revealed no abnormality. The blood-pressure was 160/100. There was some weakness of all muscle groups, which was regarded as compatible with her asthenic state, as no other abnormality was found on examination of the central nervous system. Examination of the abdomen revealed a uniform firm enlargement of the liver, the edge of which was palpable four fingers' breadths below the right costal margin. There was no enlargement of the spleen and no ascites. A provisional diagnosis of haemochromatosis was made and subsequently confirmed by investigations, the details of which are set out in the Table. Her diabetic condition was satisfactorily controlled by a diet of carbohydrate 265 gm, protein 111 gm, fat 140 gm (2,757 calories) with 48 units of soluble insulin before the morning and evening meals. She was discharged from hospital five weeks after admission, having gained one stone in weight. She resumed her work and carried on without difficulty until April 1947, when she developed ketosis after a sudden attack of gastro-enteritis. She was readmitted to hospital, responded rapidly to treatment, and was discharged within a fortnight to resume work. At this stage she had resumed her former diet and insulin dosage. No significant alteration has been noticed in the size of her liver, and at the time of writing she states that she is feeling perfectly well. A decrease in the intensity of pigmentation has occurred since she was first seen, this is possibly due to the gain of two and a half stone in weight.

Case 3 A man aged 48 years, by occupation a boiler attendant, was first seen at the Alfred Hospital on March 25, 1946. He complained of lassitude and tiredness for about three months. He had also noticed cramps in the legs for six weeks, during which period he had lost over one stone in weight. Thirst and polyuria had been present for only three or four weeks. He was unaware of any change of colour, although he was obviously heavily pigmented. It was impossible by interrogation of the patient or his relatives to determine how long this had been present. The family history disclosed no evidence of pigmentation or diabetes mellitus in the preceding two generations. His personal history revealed no illnesses of any sort since childhood, apart from a fracture of the right femur 12 years previously. He admitted to taking three or four glasses of beer a day for many years.

Examination at the time of admission revealed a wasted, middle-aged man whose skin showed generalized pigmentation more or less evenly distributed over the face, trunk, and limbs. There was no evidence of abnormal loss of hair. No abnormality was detected on examination of the cardiovascular or respiratory systems. The blood-pressure was 100/70. No abnormality was detected on examination of the central nervous system. Examination of the abdomen revealed some generalized distension, due to extreme enlargement of the liver, the edge of which was palpable five fingers' breadths below the right costal margin. The surface was uniformly firm, no nodules being felt. The spleen was not palpable, and no other abnormality was detected. A tentative diagnosis of haemochromatosis was made and subsequently confirmed by skin biopsy, glucose tolerance tests, and other investigations which are set out in detail in the Table. His diabetes was soon satisfactorily controlled by a diet of carbohydrate 200 gm, protein 100 gm, fat 175 gm (2,775 calories), with

TABLE

Case number	1	2	3	4	6	7
Age (years)	54	47	48	54	62	50
Sex	F	F	M	M	M.	M
First seen	July 1939	March 1946	March 1946	September 1946	September 1946	February 1947
Family History	Maternal uncle	Nil	Nil	Nil	Nil	Nil
Diabetes	Nil	Nil	Nil	Nil	Nil	Nil
Pigmentation	Nil	Nil	Nil	Nil	Nil	Nil
Past History	Rheumatism after pyorrhoen	Nil	Nil	Otitis media 1914, left mastoidectomy 1939	Excessive alcohol for years	Nil
Initial Symptoms	12 months	6 months	1 month	4 months	Nil	3 months
Diabetes	9 months	Nil obtainable	Indefinite	20 years	Indefinite	6 years
Pigmentation	Hepatomegaly	Nil	Nil	Nil	Anorexia and lassitude 6 months	Nil
Other	6 months				Dyspnoea 2 months	
Glucose Tolerance Test						
Blood sugar (mg per 100 c c)						
Fasting	320	308	336	290	100	275
$\frac{1}{2}$ hr after glucose	410	434	380	350	165	410
1	500	444	448	440	200	480
$1\frac{1}{2}$ hrs "	490	448	408	470	250	470
2	440	448	400	500	240	410
Diet Formula						
Carbohydrate (gm)	200	205	200	200	193	239
Protein	175	141	175	150	99	112
Fat	100	110	100	100	86	102
Calories	2,775	2,709	2,775	2,650	2,007	2,532
Insulin Dosage (units)						
Morning	45 soluble	48 soluble	32 soluble	24 soluble	Nil	20 soluble
Evening	40 "	48 "	32 "	24 "	Nil	10 P Z

Skin Biopsy	Haemosiderin present in section	Haemosiderin present in deeper layers of epidermis	Deposits of haemosiderin present	Haemosiderin present in deeper layers of epidermis	
Basal Metabolic Rate	+3 %	+8 %	+2 %	+15 %	
Serum calcium (mg per 100 cc)	10.0	8.0	9.6	10.6	
Serum bilirubin (mg per 100 cc)	0.3	0.2	0.2	0.4	0.2
Blood Examination					
Haemoglobin (gm per 100 cc)	11.2	12.0	14.0	15.0	16.7
Red cells (per c mm)	4,000,000	4,500,000	4,100,000	5,100,000	5,000,000
Average diameter (μ)	7.5	7.7	7.7	7.4	7.5
White cells (per c mm)	7,500	5,700	4,500	11,200	6,000
Differential count	Slight lympho-cytosis	Normal	Slight granulo-penia	Normal	Normal
Film	Normal	Slight macrocytosis	Some anisocytosis	Normal	Normal

* A fractional test meal, barium meal, and urea clearance were performed in Cases 1, 2, 3, and 4, and in no instance showed any departure from normal

† X ray of chest was performed in all cases and in no instance was any abnormality seen nor was any significant alteration observed in the outline of the heart

40 units of soluble insulin before the morning and evening meals. His general condition improved considerably, he was discharged after five weeks, and resumed his work as a boiler attendant. He has continued this occupation for the past 12 months without any loss of time from work. His insulin requirements, under the influence of exercise, have fallen to 28 units twice daily. There has been no appreciable change in the size of the liver and he feels perfectly well.

Case 4 A man aged 54 years, a clerk, was first seen at the Alfred Hospital on September 26, 1946, complaining of loss of weight, thirst, and polyuria for four months. The onset of his symptoms coincided with an attack of abdominal colic which lasted 24 hours, and never recurred. From that time he slowly lost strength. He had been aware of pigmentation of his skin for at least 20 years, but both he and his relatives considered that there had been no alteration in intensity for many years. There was no family history of pigmentation or diabetes mellitus. His past history was clear, apart from a bilateral otitis media in 1914. An exacerbation of this complaint in 1939 was treated by left mastoidectomy, after which the hearing in his left ear had been considerably reduced. His consumption of alcohol was limited to an occasional glass of beer.

Examination at the time of admission revealed a thin, middle-aged man with a slaty-brown pigmentation of the skin, more marked on the face and hands. There was an obvious patch of pigmentation present on the soft palate. Examination of the cardiovascular and respiratory systems revealed no abnormality. The blood-pressure was 130/75. Examination of the abdomen showed considerable enlargement of the liver, the edge of which was palpable three fingers' breadths below the right costal margin, its consistency was firm and no nodules could be felt. The tip of the spleen was palpable on deep inspiration. No other abnormalities were detected in the abdomen. Routine examination of the central nervous system showed no evidence of disorder. The area of the left mastoid operation was soundly healed and there was no evidence of discharge from the ear. A tentative diagnosis of haemochromatosis was made, and subsequently confirmed by skin biopsy and glucose tolerance tests. After suitable preparation with vitamin K, a liver biopsy was performed which showed changes typical of haemochromatosis (Plate 18, Fig. 1). The other investigations performed are set out in detail in the Table. His diabetic condition was brought under control by a diet of carbohydrate 250 gm, protein 100 gm, fat 175 gm (2,975 calories), with 24 units of soluble insulin before the morning and evening meals. He was discharged from hospital after four weeks and resumed his work as a clerk. He has continued this occupation without interruption since. He is free from symptoms and states that he feels perfectly well. On the return of weight to normal, his diet was reduced to carbohydrate 250 gm, protein 85 gm, fat 120 gm (2,420 calories), and his insulin dosage modified to 28 units in the morning and 24 units in the evening.

Case 5 A man aged 50 years, by occupation a barman, was admitted to the Alfred Hospital on April 19, 1947. He stated that he had been quite well until eight weeks previously, when he had noticed that his abdomen was enlarging and that he had difficulty in bending. The swelling of his abdomen had increased and he had become aware of shortness of breath on exertion and some loss of weight. For many years he had consumed excessive quantities of beer and had frequently vomited in the early morning. For the remainder of the day his appetite had been good and there were no symptoms of dyspepsia. In 1921 he had contracted syphilis for which he had received treatment for

some years and his Wassermann reaction was repeatedly negative. The family history revealed no evidence of diabetes or pigmentation. Apart from injuries received in the First World War, which were of no significance, he had suffered from no illnesses since childhood.

Examination at the time of admission revealed a middle-aged man with a florid complexion and a dusky colour of the trunk. The heart was slightly enlarged on clinical examination and a soft apical systolic murmur was heard. The blood-pressure was 160/120. No abnormality was observed in the lungs, other than a few fine moist sounds at both lung bases. The abdomen was distended and tense, the umbilicus being flattened, and enlarged veins were obvious over the costal margins. Shifting dullness and a fluid thrill were elicited. Because of the distension of the abdomen it was not possible to determine the size of the liver. Pitting oedema was apparent in both feet and legs up to the knees. A provisional diagnosis of cirrhosis of the liver with chronic gastritis and ascites was made. His urine at this stage gave a faint reduction of Benedict's solution. The serum-protein was 7.5 gm per 100 c.c. (serum-albumen 3.6 gm and serum-globulin 3.9 gm per 100 c.c.). The haemoglobin was 75 per cent. Paracentesis abdominis was performed shortly after admission and 13 pints of straw-coloured fluid (sp. gr. 1.002) were slowly withdrawn, with relief to the patient. Two days later, before any further investigations were performed, he suffered a severe haematemesis, lapsed into coma, and died within 24 hours.

At autopsy the significant findings were as follows: The stomach contained about two pints of blood with well-developed oesophageal varices. The duodenum showed two small ulcers on the anterior and posterolateral surfaces of the first part, but no blood was found in the duodenum. The liver was reddish-brown in colour and the surface covered with small nodules. Cut section showed the same discoloration and a mosaic pattern of nodules intersected by bands of fibrous tissue. The pancreas was hard and the cut surface showed a reddish-brown pigmentation with increase in fibrous tissue. The testes were atrophic. Microscopic examination revealed an advanced portal cirrhosis with pigment scattered in the portal connective tissue and in the liver cells. Prussian Blue stains proved this to contain iron (Plate 18, Fig. 2). The pancreas also showed some increase of interacinar fibrous tissue, and a diffuse granular pigmentation was present between and in the pancreatic cells. This pigment also gave a positive Prussian Blue reaction (Plate 19, Fig. 3). It must be unusual for a patient with haemochromatosis to die from the effects of the liver lesions before diabetes is evident clinically. In this case there was enough evidence of alcoholism to cause cirrhosis, and perhaps thus aggravated an already existing lesion. It is not suggested that the portal cirrhosis was the primary lesion nor that it was the cause of the haemochromatosis.

The following two cases were seen within a period of six weeks at the Heidelberg Military Hospital. In both instances the diagnosis was proved by aspiration biopsy of the liver.

Case 6. A man aged 62 years was admitted to hospital in October 1946. He had previously been treated in hospital for pneumonia in September 1946, after which he had noticed anorexia, lassitude, and dyspnoea on slight exertion. The past history revealed that he had worked as a barman for many years and had been a heavy drinker. He had suffered from no illnesses of significance. There was no family history of diabetes mellitus.

On admission slight cyanosis of the lips was noticed. The heart was not

enlarged to clinical examination and the sounds were clear. The blood-pressure was 140/81. Examination of the lungs showed some impairment of percussion over both bases, and fine crepitant râles were audible in both lower lobes. Examination of the abdomen revealed a smooth firm enlargement of the liver, the edge of which was palpable two fingers' breadths below the right costal margin. The spleen was not palpable. An electrocardiogram showed low-voltage tracings in every lead and changes in the ST segments consistent with myocardial ischaemia. A provisional diagnosis of congestive cardiac failure was made and he was treated with tab. digitalis folia gr 1 thrice daily, and rest in bed. His general condition improved, but the enlargement of the liver persisted. It was noticed that dark-brown pigmentation was present about the neck and arms and that his face and trunk were of a slaty-grey colour. A bronze tinge was apparent on his legs and the medial sides of the thighs. His skin was dry and scaly and his hair showed thinning over the scalp and eyebrows. The axillary hair was normal, but the pubic hair scanty. Interrogation of the patient failed to elicit any information as to the duration of his pigmentation. A provisional diagnosis of haemochromatosis was made and was confirmed by the results of a liver biopsy performed in January 1947 (Plate 19, Fig. 4). The details of other investigations are set out in the Table. He was treated with a diet of carbohydrate 193 gm, protein 86 gm, fat 99 gm (2,007 calories), after which repeated urine examinations failed to reveal any trace of reducing substance. He was discharged from hospital on this diet without insulin.

Case 7. A man aged 50 years was admitted to Heidelberg Military Hospital in February 1947. He complained of thirst, polyuria, loss of weight, and lassitude for the previous three months. He had suffered from no serious illnesses. After an accident in 1940 for which he received treatment with an infra-red lamp, he had noticed that the skin of his legs had become darker in colour. There was no family history of diabetes mellitus or pigmentation.

Examination revealed a man looking considerably older than his stated age. A patchy diffuse bronze pigmentation was obvious over the face and legs. No abnormality was detected on clinical examination of the cardiovascular system. The blood-pressure was 140/80. No abnormality was found on examination of the lungs. A smooth, firm enlargement of the liver was observed, the edge was palpable three fingers' breadths below the right costal margin. No other abnormality was found on examination of the abdomen. A provisional diagnosis of haemochromatosis was made and later confirmed by aspiration biopsy of the liver, which showed the typical picture of haemochromatosis (Plate 20, Fig. 5). The results of other investigations are set out in detail in the Table. His diabetic condition was easily brought under control with a diet of carbohydrate 229 gm, protein 102 gm, fat 112 gm. (2,532 calories), and 20 units of soluble insulin with 10 units of protamine zinc insulin each morning before breakfast. His symptoms subsided rapidly, he gained in weight and strength, and was discharged from hospital feeling quite well.

Discussion

Frequency of occurrence of haemochromatosis. Sheldon (1935), from an exhaustive study of the literature up to 1934, considered that 311 cases of haemochromatosis had been described, he excluded a further 34 for various reasons. In his series he admitted only 13 cases in women, excluding a further nine in

which he considered the diagnosis to be doubtful or wrong. No similar comprehensive study of the literature has been made in the past 13 years and although several series of appreciable numbers have been published, the disease is still regarded as a rarity. Butt and Wilder (1938) gave an account of 30 patients admitted to the Mayo Clinic in the previous 15 years, in all of whom the diagnosis had been made during life. Both in this series and in Lawrence's (1940) experience the rarity of the disease in women is emphasized, the proportions of women to men being 1 to 29 and 1 to 28, respectively. The incidence of haemochromatosis in the Alfred Hospital over the past 12 years has averaged 1 in 6,000 admissions, and the sex incidence has been three women to 10 men. These figures seem sufficiently unusual to warrant record. Although Sheldon makes the following observation—'A curious feature is the tendency for a number of cases to be seen within a short while in certain places, after or before long periods in which the disease is hardly ever encountered', it is possible that the disease is of greater frequency than has hitherto been recognized and that, largely due to the stimulus of Sheldon's work and the interest aroused thereby, cases are now recognized where previously they would have been overlooked. Certainly it seems from our experience that the condition is more frequent than previous records indicate.

The value of live biopsy in haemochromatosis Aspiration biopsy of the liver has been performed in three of the cases reported in the present paper. In addition, biopsy has proved the diagnosis in three other cases encountered elsewhere in Melbourne, one being a woman. The technique employed has been described by one of us (King, 1948). Useful information can be obtained before actual histological examination of the liver specimen is made. In the first place, the liver feels abnormally hard to the exploring needle, whose introduction is accompanied by a sensation of grittiness. Secondly, owing to the excessive fibrosis present in the liver the specimen obtained is always ragged and readily fragments, which may present a problem in embedding and sectioning. In one case the core of liver tissue obtained showed a deep brown colour typical of the liver in haemochromatosis. Sufficient material is usually obtained to show distortion of the normal liver architecture by broad bands of pigment-containing connective tissue, while pigment is always seen in the liver cells. On all occasions a Prussian Blue stain has been carried out to confirm the presence of iron-containing pigment. Aspiration biopsy of the liver can be a definite help in diagnosis, particularly in those cases where sugar is not found in the urine or is present in only very slight amounts. By this means, a correct diagnosis can be made at an early stage in doubtful cases, and it is considered likely that this mode of investigation will show the disease to be more common than it is thought to be at present. Histological examination of the tissue obtained gives a picture which is typical of the condition. It is necessary to insist that liver puncture should be performed in hospital and only after careful preoperative preparation. Owing to the technical difficulties which may be encountered because of the excessive fibrosis of the liver, it is a procedure which should be practised only by someone experienced in the technique. In none

of the six biopsies performed for haemochromatosis reported here has any complication occurred

Diabetic control in haemochromatosis Sheldon stated that in 77 per cent of the cases which he reviewed, the first symptom was one of the triad diabetes, pigmentation of the skin, and enlargement of the liver. It is, however, wise to emphasize that diabetes may not be the initial symptom and that it may not produce florid symptoms for a considerable time after the onset of the other signs of the disease, such as pigmentation of the skin and hepatomegaly. In no instance in our experience have we, as yet, encountered difficulties in the control of the diabetic state nor have we observed sudden or violent fluctuations in the insulin requirements of any case. The ketosis in Case 2 occurred at a stage when a mild epidemic of gastro-enteritis was evident and it is reasonable to assume from the symptoms and course of her condition that infection was responsible, rather than an intrinsic disturbance of carbohydrate metabolism.

An observation of some importance has been made from the study of liver glycogen in the material obtained by liver biopsy. Previously, as liver sections have been obtained only at autopsy, this has not been possible. By fixation in Masson's fluid of the tissue removed by liver puncture, it is easy to demonstrate the presence of glycogen in liver cells by appropriate staining. In view of published statements of the difficulties of diabetic control and sudden attacks of hypoglycaemia, it is of interest to record that in all six cases in which biopsy was performed the liver cells showed a normal content of glycogen. In only three of those cases was insulin being administered at the time of biopsy.

Conclusions

1 Seven cases of haemochromatosis, including two examples in women, are described

2 Haemochromatosis probably occurs more frequently than has hitherto been suspected

3 The value of aspiration liver biopsy as a means of early diagnosis is emphasized

4 In six cases biopsy demonstrated a normal glycogen content of the liver cells

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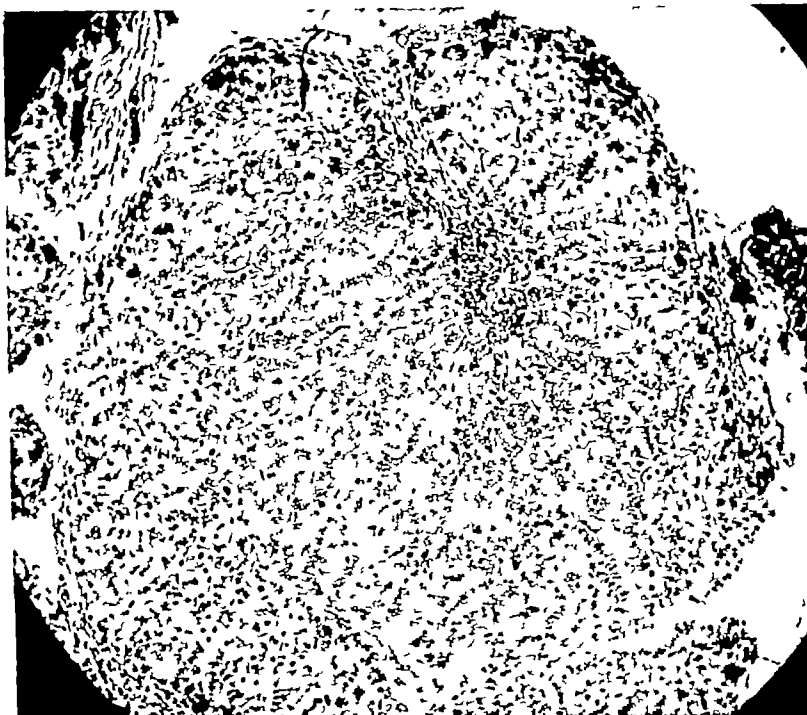


FIG 1 Case 4 Aspiration biopsy specimen of liver, showing haemosiderin in liver cells and in portal tracts (Haemotoxylin and eosin, $\times 140$)

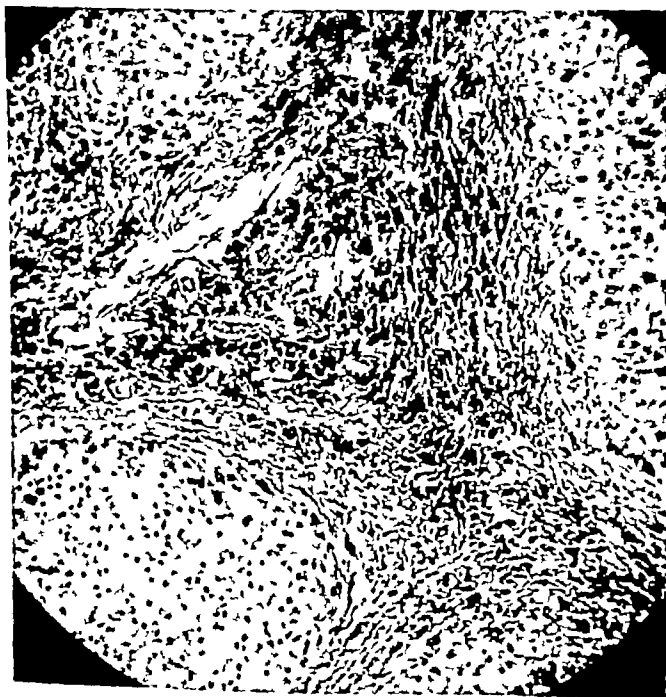


FIG 2 Case 5 Liver showing portal cirrhosis and collections of pigment in the region of the portal tracts. Scattered granules

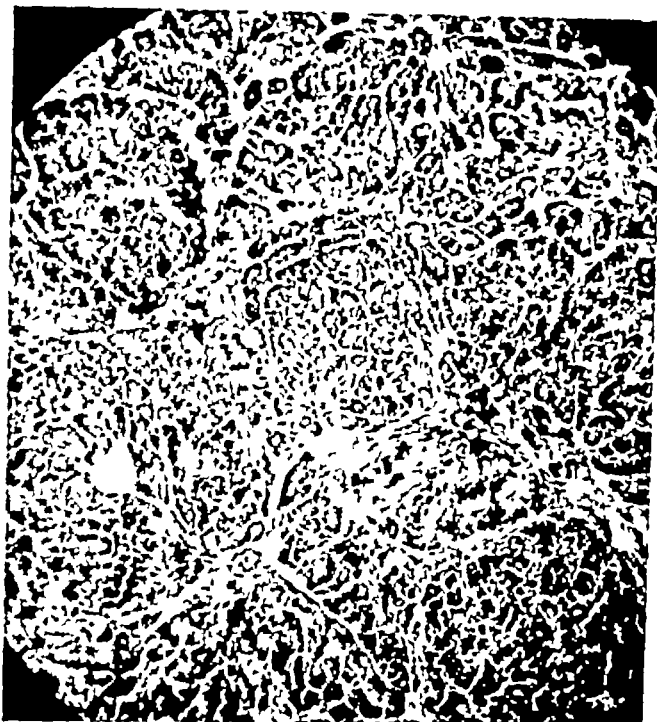


FIG. 3 Case 5 Pancreas, showing increased fibrous tissue with iron containing pigment in acinar cells and fibrous tissue (Prussian blue stain, $\times 130$)

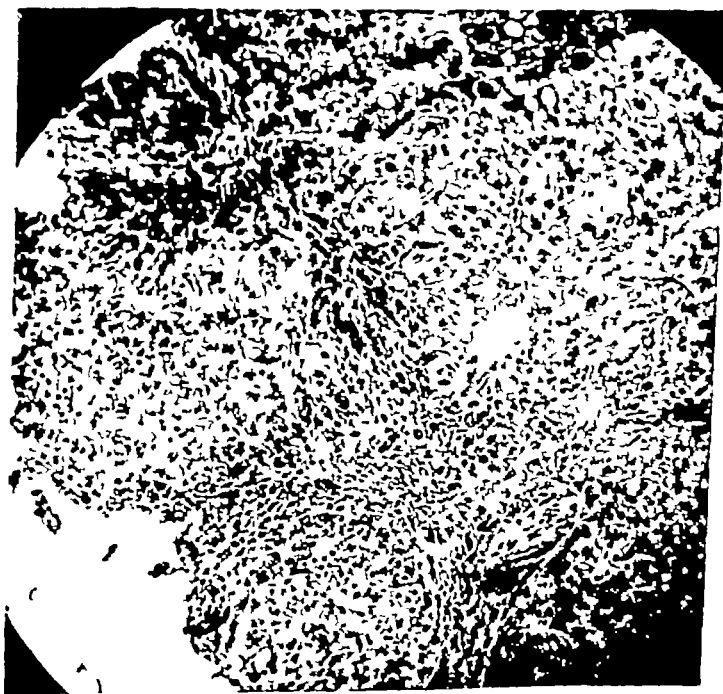


FIG. 4 Case 6 Aspiration biopsy specimen of liver, showing cirrhosis with pigment in the portal tracts and liver cells. Evidence of fatty change seen in some of the liver cells (Haematoxylin and eosin, $\times 140$)



FIG 5 Case 7 Aspiration biopsy specimen of liver, showing typical findings of haemochromatosis (Haematoxylin and eosin, $\times 140$)

PULMONARY EOSINOPHILOSIS¹

BY R. VISWANATHAN

With Plate 21

Introduction

PULMONARY EOSINOPHILOSIS is a clinical condition characterized chiefly by cough, paroxysms of dyspnoea, a raised total white-cell count with persistent and absolute eosinophilia, and frequent systemic manifestations such as fever, lassitude, and loss of weight. It is only within the last 10 or 15 years that this syndrome has been recognized as a separate entity. It is proposed to begin the present paper with an historical review, followed by a general description of the disease based on the literature, and then to record observations on a series of 207 cases. Finally, the nature of the condition will be discussed.

Historical Review

In 1935 a patient was referred to the writer as suffering from miliary tuberculosis because of a high remittent type of fever, cough, and disseminated shadows in the X-ray of the lung. The sputum did not contain tubercle bacilli. Blood examination showed a high leucocytosis and massive eosinophilia. The condition ran a benign course, though it took over nine months for all the symptoms to clear. Later, further cases of a similar nature were seen by the writer and a note describing them was published in the annual report for 1939 of the King George Hospital, Vizagapatam, India.

Under the title *Pseudotuberculosis of the lung with massive eosinophilia*, Frimodt-Møller and Barton (1940) reported 175 cases, with nodular shadows in X-rays of the lungs and over 20 per cent. of eosinophils in the blood.

Bass (1941) reported three cases in children in the United States of America. All had massive eosinophilia and miliary infiltration of the lungs. One patient died of bronchopneumonia. In the other two, the condition persisted for years with fever, palpable spleen, and lymphadenopathy, but they eventually recovered.

Weingarten (1943) reported cases of what he called tropical eosinophilia, successfully treated with neoarsphenamine injections. He described 81 cases presenting lassitude, loss of weight, fever, cough, asthmatic attacks, massive eosinophilia, and mottled shadows in the X-ray picture of the lungs. Patients of several races, all ages, and both sexes were affected. He emphasized the environmental factor, as practically all his cases were either from the coastal districts of India or had lived near the coast prior to the onset of the disease.

¹ Received June 1, 1948

Simmons (1943) observed 35 cases during the course of nine years in India. His patients had cough, fever, enlargement of the liver, lung mottling, and eosinophilia. He used the term benign eosinophil leukaemia for this condition.

Chaudhuri (1943), in his editorial review, after reporting a case in India, thought that the paroxysms of cough, eosinophilia, and pulmonary infiltrations were the result of an allergic response to some antigen.

Chakravarty and Roy (1943) reported from Calcutta one case which had urticaria in addition to other symptoms.

Shah (1943) discovered the disease in an Indian patient, with sudden onset of high fever, which was mistaken first for malaria and then for influenza.

Treu (1943) reported two cases in India successfully treated with neoarsphenamine injections.

Heilig and Visweswar (1943), after describing two cases from Mysore, concluded that the disease is possibly allergic in nature.

Vaidya (1943) saw six cases in Bombay from 1929 to 1934. They were all treated with neoarsphenamine. Two of these patients had repeated relapses.

Emerson (1941) reported a case of tropical eosinophilia in a young American of 30 years who, after living in India from 1937 to 1942, had just returned to the United States. The patient was successfully treated with carbarsone.

Parsons-Smith (1944) observed the condition in a male European in Egypt.

Leishman and Kelsall (1944) saw eight cases in a Military Hospital in India. All the patients were Anglo-Indians or Indians who had been living in coastal districts since childhood. Neoarsphenamine injections proved successful in all cases.

Carter, Wedd, and D'Abrera (1944) detected different varieties of mites in the sputum of 17 out of 26 persons in Ceylon, 24 of whom were receiving treatment for various respiratory disorders. In three of the mite-infested patients an eosinophilia of 38 to 66 per cent was observed.

Of the six cases reported by Treu in 1944 in India, one had no lung symptoms, but had swelling of lymphnodes and fever. In his series two members of one family developed the disease.

Ritchie (1944) discovered the condition in an African from Tanganyika.

Soyza and Jayawardena (1945) gave an account of investigations conducted in 25 Ceylonese patients who showed high eosinophilia, symptoms of respiratory disorder, and had mites in the sputum. All responded satisfactorily to arsenical treatment.

Apley and Grant (1945) made a critical review of tropical eosinophilia, as seen in England, after encountering four more cases subsequent to their previous report of one case (1944). In their opinion tropical eosinophilia and Löffler's syndrome are indistinguishable.

Lal (1945), after reporting 15 cases from Bengal, concluded that the syndrome was not a separate clinical entity, but was of the nature of allergic pneumonia.

Hirst and McCann (1945) found the condition in a United States naval officer who developed symptoms while stationed in Samoa. Injections of

neocarsphenamine cured the condition, although it had persisted for two years. They could not find the cause.

Patel (1945) reviewed 49 cases from Bombay, of whom 37 were male and 12 female. In his opinion the condition is an allergic manifestation, the pulmonary interstitial tissue being sensitive rather than the bronchi.

Van der Sar and Hartz (1945) saw three cases in Curaçao. In one they found microfilaria in the enlarged lymphnodes. Arsenical medication cured all the patients. They considered that they had demonstrated filariasis as the cause of the condition.

McGuire (1945), in a discussion on periarteritis nodosa, referred to two American soldiers who developed tropical eosinophilia in an island in the south-west Pacific.

Menon (1946) observed that the disease has a wide distribution geographically, though the incidence may be higher in certain localities. He laid down certain useful diagnostic criteria, and also offered some experimental evidence, based on guinea-pig inoculation with blood, in support of the infection theory which he had postulated in his first paper (1945).

Van der Sar (1946), under the title pulmonary acariasis, reported eight cases in all of which he had found mites in the sputum. The first four conformed to the description of pulmonary eosinophilosis, while the remaining four were possibly cases of Löfller's syndrome. He wondered why mite infestation should produce two different types of manifestation.

Irwin (1946), after reviewing some of the previous reports on the subject, gave details of two patients who developed the disease while serving in the south-west Pacific theatre of war. Neither had microfilaria in the blood. Both patients, however, gave positive reactions to intradermal skin tests with *Dirofilaria immitis* antigen. Irwin suggested that all future cases should be tested for microfilaria.

D'Abrera and Stork (1946) reported the combination of a positive Wassermann reaction with a doubtful or negative Kahn reaction in 68 per cent of cases of this syndrome. They also noticed reversal of serological reactions after treatment.

Hunter (1946) discovered the syndrome in a European after his return to England from Nigeria.

Jhatakia (1946) observed 140 cases of eosinophilic lung. He recorded the syndrome as occurring in more than one member of a family. On the basis of his findings he grouped the cases as ambulatory, acute, and chronic types.

General Description of the Disease based on Previous Reports

Actiology. During recent years 685 cases, conforming to the description of this clinical condition, though under different names, have been reported. Inquiries made by the writer from several medical men and women in different parts of India suggest that many more cases of pulmonary eosinophilosis have been observed by general practitioners. Most of the recorded cases have been from India and Ceylon. A few have been reported from the United States of

America, England, North Africa, Tanganyika, China, Australia, Singapore, and south-west Pacific islands Weingarten (1943) thought that the disease was confined to the coastal districts of India Other reports, however, show that it is widely distributed throughout the country It has occurred among people from places as widely separated as Delhi, Nagpur, Lahore, and Peshawar Many of these patients have never been to the sea-coast at any time in their lives As in the majority of cases the onset, or an exacerbation of the disease, occurs during the rainy season or soon after the rains, it is possible that humidity of the atmosphere rather than nearness to the sea may be a contributing aetiological factor It cannot be considered exclusively as a tropical disease as a few cases have been reported from other parts of the world

The disease has been observed at all ages from one to 62 years The highest incidence in all the reported series has been in the 20 to 40 years age-groups, and there has been a preponderance of male over female patients All races appear to be affected There does not seem to be any constitutional or familial susceptibility. Occupation does not in general appear to bear any aetiological relationship, nor does the economic status of the individual, but reports from Ceylon (Carter, Wedd, and D'Abreu, 1944) and Bombay (Jhatakia, 1946) suggest that there is a high incidence of the disease among workers in gram stores

Ceylon workers (Carter, Wedd, and D'Abreu, 1944) have found mites in the sputum in a large percentage of cases with respiratory symptoms The mites observed were chiefly of the genera *Tarsonemus*, *Tyroglyphus*, and *Carpoglyphus* The authors suggest that mite infestation of the lung might be the causative factor at least in some cases of tropical eosinophilia A report of the finding of a solitary mite in the sputum of a patient comes from Bombay (Jhatakia, 1946) *Tyroglyphus* was also found in the sputum of cases of what was described as pulmonary acariasis by van der Sar (1946) There are, however, some outstanding difficulties in accepting the mite as the causative factor in pulmonary eosinophilosis In the first place, the majority of cases in which the Ceylon workers found mites in the sputum did not have a high eosinophilia, which is an essential diagnostic criterion for the disease Secondly, many other workers have failed to find mites in the sputum of patients suffering from the disease Thirdly, as one writer aptly puts it, it will be very difficult apart from technical considerations to prove mite infestation of the respiratory tract in cases showing lung symptoms but unproductive cough Fourthly, typical cases have been reported without cough or asthmatic attacks, but conforming otherwise to the symptomatology of the disease, and showing a favourable therapeutic response to arsenic (Treu, 1944, Jhatakia, 1946)

Pathology No reported case conforming to the description of pulmonary eosinophilosis has come to autopsy Hence the pathology of the condition is obscure Chaudhuri (1943) surmised that the mottled shadows seen in the radiographs of the lungs are probably due to infiltrations of the lung parenchyma with eosinophil cells

Clinical features Study of the clinical course of the disease suggests the

existence of two distinct types, the acute and the chronic. The vast majority of cases reported so far belong to the chronic type. The acute type can again be sub-divided into a self-limiting variety in which the condition clears up completely within a short period without treatment, and a variety in which the disease goes on to the chronic stage if untreated. In the acute type, the onset is sudden with high fever ranging from 102° to 104° F, cough, and hurried respiration, simulating an attack of acute bronchiolitis or pneumonia. Physical signs as a rule are those of acute bronchitis, but in a few cases signs of patchy consolidation are detected. Only the presence of absolute eosinophilia helps to reveal the true nature of the condition. In about 25 per cent of the cases the symptoms clear up completely without any specific treatment in four to six weeks, but the remainder pass on to the chronic stage. In the ordinary chronic type the mode of onset is gradual. General malaise, lassitude, impaired appetite, and a low-grade fever ranging from 99° to 101° F are the usual presenting symptoms. After a week or 10 days the patient begins to have a dry cough, but in some cases cough is the first symptom to be noticed. The cough is unproductive in the early stages, and comes on in paroxysms particularly at night. After a month or two the patient begins to cough up a scanty amount of viscid sputum. A fit of coughing continues until a pellet of sticky mucus is brought up. Sooner or later the patient begins to feel breathless either after a paroxysm of coughing or after any kind of physical exertion. Such breathlessness is a more frequent manifestation of the disease than asthmatic attacks, but paroxysms of expiratory dyspnoea occur in a large number of cases and are often mistaken for true asthma. In an untreated case of the chronic type the febrile period varies from a few days to two months, while the respiratory symptoms last for a year or more. In some cases, the disease continues for years in the form of periodic attacks of asthma-like paroxysms.

Physical signs in the lungs are absent during the first few weeks. Later, when the cough becomes productive, râles and rhonchi are heard at the bases of both lungs. When there is an asthmatic paroxysm, prolonged expiration and sonorous rhonchi are heard. Hyperresonance of the chest is a frequent finding in the later stages. The sputum rarely contains Charcot-Leyden crystals or Curschmann's spirals, but clumps of eosinophils are frequently seen. Enlargement of the spleen is found in about 50 per cent of the cases, particularly during the febrile period.

A few atypical cases, with presenting symptoms such as prolonged pyrexia, exhaustion, palpitations, precordial pain, lymphnode enlargement, and enlargement of the liver, occurring singly or in combination with respiratory symptoms, have been reported. The diagnosis is made in these cases by the finding of high eosinophilia and the therapeutic response to arsenic. A case has recently been reported by Elkeles and Butler (1946) of transitory pulmonary infiltrations and apical cavitation with eosinophilia, but there seems no doubt that, as the authors suggest, this was a case of Löffler's syndrome and not one of pulmonary eosinophilosis.

Laboratory findings. The changes in the blood are the most characteristic

feature of the disease. The total white-cell count varies from 12,000 to 80,000 per c mm, while the eosinophil percentage ranges between 20 and 80. Massive eosinophilia is responsible for the high leucocytosis. The absolute count of the neutrophils remains more or less constant. Immature eosinophils are rarely seen while over-mature ones are more frequently met with. Two types of eosinophils, one with well-stained coarse granules, and the other with lightly stained fine granules, are seen with equal frequency. The clinical significance of the two types is not understood. The degree of eosinophilia bears no relationship to the severity of the symptoms. The bone-marrow shows a preponderance of mature eosinophils, and the myelocytic reaction is absent. As a rule the pulmonary signs and symptoms disappear more quickly in response to treatment than the alterations in the blood.

Viswanathan and Natarajan (1945) have shown that the serum of most cases produces high titre cold agglutination of red blood-cells. Subsequent to the publication of their results 52 more sera were tested by them, of which 40 gave high-titre cold agglutination. A larger percentage of positive results was claimed by Lal in a personal communication.

D'Abrera and Stork (1946) and Menon (1946) found positive Wassermann and/or Kahn reactions in some of their cases in the absence of any positive evidence of syphilis. Menon (1946) uses the test as one of the diagnostic criteria, particularly when the serological reactions are reversed after oral administration of stovarsol.

In the majority of the cases the erythrocyte sedimentation rate is raised.

Radiographic findings. The so called typical X-ray picture of disseminated mottled shadows distributed throughout both lungs is not consistently observed. The mottling may be confined to one lung or part of one lung. It may be present only in certain phases of the disease and, therefore, X-ray pictures taken at other times may not show any changes which can be considered typical. In other cases, however, the shadows are so uniformly distributed as to suggest a haematogenous dissemination. X-ray changes are commonly seen during the febrile stage of the disease. During the later stages, only prominent bronchial markings are usually found, but in a proportion of untreated cases X-ray shadows persist for months.

Diagnosis. A history of an illness with a febrile onset and long-continued cough, breathlessness on exertion, fits of bronchial spasm, massive eosinophilia with a high total white-cell count, and mottled shadows in the X-ray of the lungs is sufficient evidence to establish a diagnosis of pulmonary eosiniphilosis. Other conditions producing eosinophilia have to be considered for purposes of diagnosis. Helminthic infestation can be excluded by systematic examination of stools or by therapeutic elimination of the possibility. Difficulty might arise when a case of true asthma with eosinophilia is encountered. In asthma, however, the total white-cell count is rarely above normal, though in some cases there may be a relative eosinophilia. Radiography of the chest does not show any of the characteristic abnormalities. A normal erythrocyte sedimentation rate and negative Wassermann reaction will also help in the diagnosis.

Asthmatic attacks are rarely relieved by arsenical injections. On the other hand, the therapeutic response of pulmonary eosinophilosis to arsenical drugs is nothing short of dramatic. Löffler's syndrome is another important condition from which pulmonary eosinophilosis has to be differentiated, but some writers are of opinion that the conditions are identical. Löffler (1936) described the syndrome as characterized by transitory migratory pulmonary infiltration associated with peripheral eosinophilia and paucity or absence of systemic manifestations. He was at first of opinion that it was a tuberculous process. Later he produced evidence to show that it was due to the pulmonary phase of ascari infestation. Engel (1937) ascribed it to inhalation of pollen from the privet shrub. Meyer (1937) thought that pollen of convallaria was the offending factor. Harkavy (1943) has reported on Löffler's pneumonia in asthmatic states. *Ascaris lumbricoides*, *Taenia saginata*, *Trichuris trichiura*, *Fasciola hepatica*, *Entamoeba histolytica*, brucella, and azosulphamide have all been incriminated in its causation. Wright and Gold (1946) add cutaneous helminths as an additional cause. Evidently Löffler's syndrome is an allergic response to a variety of allergens. The absence of systemic disturbances, the transitory and migratory nature of the pulmonary infiltrations, the rapidly fluctuating blood changes, the spontaneous disappearance of all signs without treatment, the negative Wassermann reactions, and normal sedimentation rate will enable it to be differentiated from pulmonary eosinophilosis.

Prognosis If untreated, pulmonary eosinophilosis persists for months, sometimes years, with remissions and exacerbations. Arsenic acts as a specific in the great majority of cases and response to it can be used as a diagnostic criterion. A few patients, less than 2 per cent, do not respond fully to treatment, though some amelioration of symptoms is obtained in all. Also a few cases show relapses, but most of these respond to a second or sometimes a third course of treatment. The disease of itself has not up to the time of writing produced any reported death.

Treatment A few so-called asthma specialists in India had been in the habit of using preparations of arsenic, such as Soamin and neoarsphenamine, and claiming dramatic results long before pulmonary eosinophilosis was recognized as a clinical entity. The cases of asthma that were cured by them were evidently cases of the latter condition and not true asthma. A course ordinarily consists of eight weekly injections, beginning with an initial injection of 0.15 gm. and continuing with 0.3 gm. subsequently. In milder cases a short course of four injections is found to be sufficient. Some writers claim successful results with oral administration of stovarsol or carbarsone.

Present Material

Incidence The author's observations are based on a study of 207 patients, of whom 189 were Army personnel on active service in East Bengal, Assam, and Burma. Of the latter number, 172 developed the disease for the first time while serving in the above areas, while 17 patients gave histories of previous attacks of what were described as bronchitis or asthma when they were

stationed in other parts of India. Of the remaining 18, who were civilians, 15 were from Vizagapatam, one from Dacca, one from Nagpur, and one from Delhi.

Ninety per cent of the patients in the present series were between the ages of 20 and 30 years. It would, however, be misleading to draw any conclusions regarding the age incidence of the disease in general from a series of cases drawn mostly from Army personnel who necessarily belong to the age-groups of early adult life. Of the 18 civilian patients two were women. The relative frequency of symptoms, signs, and laboratory findings is shown in the Table.

Eleven cases belonged to the acute type and five were of the self-limiting variety. The onset in the latter group was sudden with high fever, cough, and hurried respiration resembling pneumonia. Two of the patients had patchy consolidation in both lungs. The remaining three had only signs of acute bronchitis at first. One of these three developed pleurisy with a small effusion, and the aspirated fluid contained eosinophils. The blood picture was essentially that of any other case of pulmonary eosinophilosis. All the patients with the self-limiting variety of the disease recovered within three to six weeks with ordinary symptomatic treatment. The remaining six cases of the acute type also started with sudden fever of 102° to 104° F. Two had bronchopneumonic signs and four had signs of acute bronchiolitis. Though the acute symptoms subsided after a fortnight, blood changes and cough persisted until the patients were treated with arsenical injections.

The ordinary chronic type comprised 186 cases, of whom 22 patients gave a history of abrupt onset in that they could remember the day of commencement of the illness. In 11 of the 22 the disease started with what was described as a severe cold characterized by sneezing, running from the nose, slight fever, and cough. In eight patients fever ranging from 99° to 100° F. was the only symptom for over 10 days. In the remaining three of the 22 cases the onset was with a sudden attack of asthma. The disease started insidiously in the rest of the cases (164), so much so that none of the patients could say exactly when the disease commenced. As the symptomatology (see the Table) was similar to that in previously reported series, a further description is considered unnecessary. Only the symptoms observed in atypical cases and the results of certain laboratory investigations are given below.

Atypical cases. Two atypical cases had breathlessness on exertion as the only symptom. Another atypical case which came under the author's observation is of particular interest owing to the unusual radiological finding of a cavity in the centre of a densely mottled area. The onset in this patient was sudden, with high fever and cough. After a week, the fever became intermittent, ranging between 99° and 101° F., and the cough became productive with mucopurulent sputum. He rapidly lost weight, and came under the writer's observation two months after the onset of the disease. At that time a diagnosis of pulmonary tuberculosis with right upper lobe infiltration was made. The X-ray film appeared to confirm the diagnosis as it showed dense mottling in the right upper lobe with a well-defined cavity in the middle. The sputum, however, was repeatedly negative for tubercle bacilli. Blood examination showed a white-

cell count of 22,000 per c mm and 42 per cent of eosinophils. The patient was given eight weekly injections of neoarsphenamine. The temperature touched normal after the second injection and all the lung symptoms disappeared after four injections. The mottling in the radiograph completely disappeared in six weeks, leaving behind only a small thin ring shadow. At the termination of the course of injections the eosinophils were reduced to 10 per cent. At the time of discharge two months later, the X-ray of the lungs was normal and the

*Symptomatology and Laboratory Investigations in 207 Cases of
Pulmonary Eosinophilosis*

	Number of cases	Percentage
Cough	201	98
Lassitude	182	89
Breathlessness on exertion	176	85
Loss of weight	113	54.5
Fever (low intermittent)	91	44
Fever (high remittent)	6	3
Fever (high continuous)	5	2
Asthma	56	27
Sense of heaviness and pain in chest	26	12.5
Haemoptysis	9	4
Palpitation	6	2
Enlargement of spleen	74	36
Enlarged lymphnodes	2	1
Eosinophils above 2,500 per c mm	196	96
Eosinophils above 10,000 per c mm	102	49
Positive X ray findings	105	51
Raised erythrocyte sedimentation rate	64	75
	(of 85 cases)	
High titre cold agglutination	103	76
	(of 135 cases)	
Positive Wassermann reaction	32	49
	(of 65 cases)	
Positive Paul-Bunnell reaction	3	33
	(of 9 cases)	

blood showed 5 per cent eosinophilia. The sedimentation rate, which was raised at the time of admission, was found to be within normal limits.

Investigations. Microscopic and cultural examinations of both sputum and blood in 17 cases failed to reveal any specific infective organism. Investigations to establish a virus aetiology also gave negative results. Specimens of sputum of 21 patients were examined for mites by the method described by Carter, Wedd, and D'Abrera (1944). In none were mites seen. Serum-globulin was found to be appreciably raised in the three cases in which it was estimated. High-titre cold agglutination was obtained in 103 of 135 cases. The Wassermann reaction was positive in 32 of 65 cases. The Kahn test was not done in any of the cases. The erythrocyte sedimentation rate was estimated in 85 cases and was found to be raised in 64.

Routine examination of the blood of all patients admitted to the medical wards permitted the detection of cases with increased eosinophil cells in the blood. All such patients were thoroughly investigated to see if they conformed to the diagnosis of pulmonary eosinophilosis. Fourteen cases were detected

when thick blood films were examined for malarial parasites. Total and differential counts during the course of treatment, before and after each injection of neoarsphenamine, showed that the eosinophil cells as a rule increased in number at first, particularly after the first injection, and subsequently began to fall. The reduction in the cell count during the course of treatment was not so rapid as the amelioration of symptoms. Normal blood pictures were not seen until a week to a month after the completion of treatment. Some cases of asthma with high eosinophilia were given injections of neoarsphenamine. It was observed that in most of these cases the eosinophil count came down after the first injection, though symptoms were not relieved even after a full course of eight injections. Exacerbation of symptoms and a rise in the eosinophil count after an injection of 0.15 gm. of neoarsphenamine were used as diagnostic criteria to differentiate pulmonary eosinophilosis from other conditions causing eosinophilia, particularly asthma. Reduction in the eosinophil count after an injection of arsenic was noticed not only in asthma but also in helminthic infestations, which usually produce varying degrees of eosinophilia.

Report of a Case with Autopsy Findings

The following case report is of interest owing to the valuable information obtained by autopsy.

An Indian man, aged 28 years, was admitted to an Indian General Hospital, with a history of cough and occasional attacks of asthma of six months' duration. A diagnosis of tropical eosinophilia was made as a blood examination showed a total white-cell count of 28,000 per c mm. with 44 per cent of eosinophils. He was given two injections of neoarsphenamine 0.3 gm., at weekly intervals. Twenty-four hours after the second injection the patient became unconscious and developed convulsions. A diagnosis of arsenical encephalopathy was made. The cerebrospinal fluid was normal. The patient died 36 hours after the onset of cerebral symptoms. Just before death, the total white-cell count was 21,000 per c mm. and eosinophils 7 per cent.

At the post-mortem examination the upper lobe of the left lung was found to be adherent to the chest wall throughout its entire extent. The adhesions were recent and could easily be broken down. There was no fluid in either pleural cavity. There were dark reddish-brown areas scattered over the surface of both lungs, but more extensively in the left upper lobe. The cut surface showed the same multiple dark reddish-brown areas varying in size from 0.5 to 2.5 cm. in diameter. They appeared to be due to haemorrhage and not consolidation. The affected portions of the lung did not sink in water. Some looked very much like the early stage of infarction. The bronchioles showed congestion of their mucous membranes and contained bloodstained mucopurulent secretion. The brain showed punctate haemorrhages both in the white and grey matter. The mesentery showed a few areas of haemorrhage. All other organs appeared normal to the naked eye. Portions of the brain and lung were removed, under strict asepsis, and sent to the laboratory for investigation. Microscopic examination of stained sections of the lung revealed several areas of interstitial fibroblastic proliferation. Here the alveoli were lined with swollen cells and their lumina were partially or completely filled with macrophages. Some of these cells contained dark brown anthracotic pigment, others a small amount

of haemosiderin, but most contained eosinophilic granules grouped in parts of the cytoplasm. These granule-containing cells were present in large numbers in only some of the alveoli and air passages. Eosinophilic leucocytes were also seen in large numbers in the interalveolar space as well as within the alveoli. The partially consolidated areas were closely related to the terminal bronchioles. Evidence of emphysema was seen in other areas. In some of the alveoli the mononuclear cells had fused together to form very large multinucleated giant cells. The nuclei varied from 15 to 25 in number in each cell, and were all gathered together in the centre. In a few areas characteristic nodule formation could be seen (Plate 21, Fig. 1). Each nodule consisted of four or five giant cells in the centre surrounded by a cluster of mononuclear cells. Evidence of recent haemorrhage with marked engorgement of interalveolar capillaries was present.

Dr K. V. Krishnan, Professor of Microbiology, reported on the samples of brain and lung tissue as follows:

(1) Brain. The section shows congestion of brain tissue with some areas showing perivascular cells. The lung shows marked congestion, haemorrhagic areas of bronchopneumonia, and catarrhal changes in the bronchioles.

(2) The rest of the tissues were emulsified separately in normal saline under aseptic precautions. The emulsions were lightly centrifuged to throw down the grosser matter and the supernatant fluid was taken out and passed through seitz pads under negative pressure. One c.c. of the brain filtrate was inoculated intraperitoneally into guinea-pig No. 3, and 1 c.c. of the lung filtrate was similarly inoculated into guinea-pig No. 2.

Guinea-pig No. 3 died after seven days. The post-mortem findings showed that the stomach and intestines were empty, there was no peritoneal exudate, the heart had stopped in systole and contained no clot or blood, the lungs did not show any abnormality, the pericardial cavity did not show any exudate. A smear from the lung showed round cell preponderance and some wandering histiocytes. Some mononuclear cells showed immense phagocytosis of carbonaceous matter. A few eosinophils were also encountered.

Guinea-pig No. 2. Blood smears examined at intervals failed to show any increase in eosinophils over that seen before inoculation.

The haemorrhages seen in the brain and lungs of this patient were probably due to arsenical poisoning. The cellular changes in the lungs were suggestive of chronicity. The affected areas were discrete and scattered, and interstitial tissue was mainly involved. Some of the adjacent alveoli also showed cellular infiltration. The cells were chiefly eosinophilic monocytes and eosinophilic polymorphs. The most striking lesion seen was the tubercle-like nodule with a group of giant cells in the centre and a cluster of monocytes surrounding it. It was definitely not a tuberculous lesion, as these peculiar giant cells and mononuclears are never found in tuberculosis. The histopathological appearances in this case were suggestive of an infective process rather than of an anaphylactic reaction. The lesions were peribronchial and not perivascular. Their nature suggested that infection in pulmonary eosinophilosis is probably by inhalation and that the infecting agent enters the peribronchial tissue and sets up an inflammatory process involving the interstitial tissue mainly and the alveoli partially. Discrete scattered areas of cellular infiltration, monocytic and eosinophilic, are produced. When the process becomes chronic, nodules containing giant cells and monocytes are formed. The disseminated mottled

shadows seen in the radiographs of cases of tropical eosinophilia are probably due to such areas of cellular infiltration with monocytes and eosinophils. They usually last for only a short period but in some cases the mottling lasts for months.

Discussion

Widely divergent views have been expressed regarding the nature of pulmonary eosinophilosis. Two fundamental questions are—

- (1) Can this symptom-complex be considered to be a distinct clinical entity?
- (2) Is it an infective or an allergic process?

As regards the first question the answer is in the affirmative. It is no doubt true that eosinophilia occurs in a variety of conditions such as intestinal helminthiasis, hydatid disease, certain skin diseases, Hodgkin's disease, periarteritis nodosa, urticaria, asthma, and certain infectious diseases such as scarlet fever. Massive eosinophilia is also found in cases of trichiniasis, and in some cases of filariasis. A combination of transient pulmonary infiltrations with high eosinophilia is also found in all those conditions which are included under the generic name of Löffler's syndrome. Pulmonary eosinophilosis cannot be included in any of these categories because of the consistently occurring combination of fever, loss of weight, cough, breathlessness, and asthmatic attacks, associated with signs of pulmonary infiltrations and persistent massive eosinophilia. Pulmonary eosinophilosis is, therefore, a distinct clinical entity.

The second important question is whether pulmonary eosinophilosis is an infective process due to a specific, arsenic-sensitive organism, or whether it is an allergic manifestation in response to different allergens. Eosinophilia and asthmatic attacks are the points put forward in favour of allergic origin. Ratner (1943) was of opinion that leucopenia is so characteristic of true serum sickness, serum allergy, protracted anaphylaxis, and drug allergy, that a fall in white-cell count can be considered as almost pathognomonic of allergy. While leucopenia occurs in the early stages, eosinophilia is characteristic of the chronic oft-repeated expressions of allergy. In his opinion, eosinophilia is never manifest in the early allergic phase. If the symptom complex of pulmonary eosinophilosis is an allergic response there should be no eosinophilia in its early stages. Cases of sudden onset with no previous history of any type of allergic manifestation were found to have massive eosinophilia from the beginning. It is also said that during the allergic phase, as for instance in the beginning of an asthmatic attack, there is a sudden fall in the white-cell count as well as in the eosinophil percentage. In pulmonary eosinophilosis, on the other hand, both are usually raised during an exacerbation.

Experimental work of Menon (1946) affords confirmation of the assumption that pulmonary eosinophilosis is not an allergic response. Injection of blood from a patient into a guinea-pig produced initial eosinophilia and secondary leucocytosis in 10 days. He argued that the changes were not due to anaphylaxis because only one injection of blood was given, and leucopenia and not leucocytosis is the usual finding in hypersensitive states. He assumed that

the blood of the patient contained material which was responsible for these changes on animal inoculation

In five cases of accidental death among soldiers who were apparently in good health, Mayenburg (1946) found eosinophilic infiltrations and giant cells with multiple nuclei in the lungs. He also noted eosinophilic bronchitis and eosinophilic bronchiolitis. He concluded that Löffler's infiltrations may be real eosinophilic bronchopneumonias originating from bronchogenic infection. Mayenburg's cases were in all probability cases of pulmonary eosinophilosis.

In the case reported on page 266, the peribronchial lesions, with eosinophilic infiltration of the interstitial tissue and some alveoli, and the presence of giant cell nodules in relation to the bronchioles are suggestive of a bronchogenic infective process.

A positive Wassermann reaction, obtained in many cases of tropical eosinophilia by Menon (1946) and D'Abrera and Stork (1946), with reversal of serology after arsenical medication, is also in favour of infection with an arsenic-sensitive organism.

The findings by the Ceylon workers and by van der Sar (1946) of mites in the sputum of patients with asthmatic symptoms and eosinophilia has given rise to the speculation that mite infestation of the respiratory tract is the cause of pulmonary eosinophilosis. Carter and D'Abrera (1946) have produced in Toque monkeys irregular and spasmodic cough and fluctuating eosinophilia by intratracheal introduction of mites. As against this theory of mite infection are the negative findings of most other writers. There is of course the possibility of a mite-borne organism and not the mite itself being the causative factor. The mite is a vector for other diseases such as typhus. It is possible that the organism of eosinophilosis is also carried by mites and introduced through the respiratory tract or through the skin. It would be unprofitable to speculate on the nature of the organism without definite evidence. Viswanathan (1945) drew a parallel between this condition and atypical pneumonia by the finding of high-titre cold agglutination along with pulmonary infiltration in both conditions. Since atypical pneumonia is considered to be due to a virus infection it is possible that pulmonary eosinophilosis may also be a virus disease.

Summary

- 1 The literature on pulmonary eosinophilosis, otherwise known as tropical eosinophilia, is reviewed
- 2 Aetiological factors are discussed and the symptomatology described
- 3 The findings in 207 cases are analysed
- 4 A case is described with autopsy findings
- 5 That it is a separate clinical entity is established
- 6 The pathogenesis is discussed, and the balance of evidence found to be in favour of an infective process

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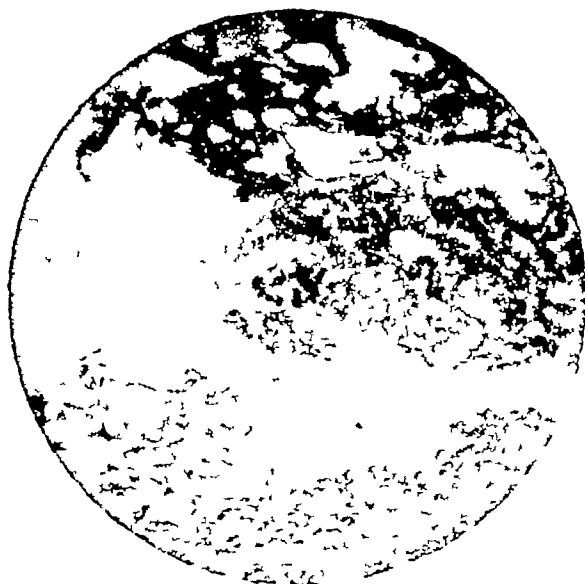


FIG 1 Photomicrograph of lung from case described on page 266. Note the nodule in the centre, with a group of giant cells surrounded by monocytes (low power)



FIG 2 Centre of the same nodule under high power magnification showing the giant cells

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A REVIEW OF ANTIHISTAMINE DRUGS¹

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Introduction

THE work of Dale (1920, 1929) and others has provided convincing evidence in favour of the theory that anaphylaxis is due to the combination of antigen with antibody inside the cells of the body, which are thus damaged. Some of the symptoms may be directly due to this damage, but many of the most dramatic effects appear to be due to the release of toxic substances from the damaged cells. Histamine is the best known of these substances, but is not the only one. Anaphylaxis is associated with an increase in the clotting time of the blood due to the release of heparin. Another substance which is known to be released during anaphylaxis is called 'the slow reacting substance' because of its slow action on plain muscle. The theory that histamine plays a part in anaphylaxis was put forward by Dale and Laidlaw (1910), and the evidence has often been reviewed (Dragstedt, 1941, Feldberg, 1941, Rocha e Silva, 1942, Code, 1944, Rose, 1947). Histamine was first prepared by Windaus and Vogt (1907). Its occurrence under natural conditions was established by Barger and Dale (1910), who found it in extracts of ergot and intestinal mucosa, and Ackermann (1910), who showed that it could be produced by bacteria. It immediately attracted attention because of its great pharmacological activity. Dale and Laidlaw (1910) noted that the effects of its injection were like those of anaphylaxis. In both states there was contraction of smooth muscle, dilatation and increased permeability of capillaries, a fall in blood-pressure, and increased secretion by various glands.

The action of histamine on man has been studied by various workers. Lewis (1927) described in detail the triple response of the skin to histamine and emphasized its resemblance to allergic urticaria and to the effects of various other forms of injury. Weiss, Robb, and Ellis (1932) gave a detailed description of the effects of its intravenous injection. In man, as in cats, the most striking action is capillary dilatation, and the effects on smooth muscle are less important. They noted that the administration of histamine did not produce bronchospasm in normal human beings, but only in asthmatic subjects, and Curry (1946) confirmed this result. There is some evidence that histamine is concerned in the production of itching and cutaneous pain (Rosenthal and Minard, 1939, Code, Keating, and Leavitt, 1948). Rothman (1941) has pointed out that though histamine in a dilution of one part in 1,000,000 will cause

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appeared so rapidly that no rise of histamine concentration was detected in the venous blood. This confirms the work of Rose (1940), who found that when histamine was given subcutaneously the blood-histamine did not rise, and might even fall. When histamine is given intravenously a small proportion is excreted as free histamine in the urine during the next six hours (Adam, 1948), but the body destroys or retains the major part (Gaddum, 1948). In the experiment of Adam and Hunter mentioned above, histamine was detected in the urine though not in the blood. Estimations of histamine in the urine should therefore be a more sensitive indication of the release of histamine in the body than estimations of histamine in the venous blood, but the results obtained so far have not been encouraging.

The best evidence that histamine is released during anaphylaxis appears in experiments with animals. Watanabe (1931) showed that anaphylaxis caused a fall in the histamine content of the lungs of guinea-pigs and livers of dogs. Bartosch, Feldberg, and Nagel (1932) detected a histamine-like substance in the perfusate of sensitized guinea-pig's lung when antigen was added. In the same year Dragstedt and Gebauer-Fuelnegg detected a similar substance in the lymph coming from the liver of the dog during anaphylaxis. It has also been shown that histamine is liberated when antigen is added to a salt solution in which sensitized tissues are suspended (Schild, 1939). Much work has been done by such methods and there is now no doubt that histamine is liberated during anaphylaxis in animals in sufficient quantities to account for most of the symptoms. This conclusion is confirmed by the work with antihistamine drugs discussed below.

Most of the experimental techniques mentioned above are not easily applied to man. The direct experimental study of anaphylaxis in man is dangerous, and attention has been directed to various allergic conditions which are probably similar in their mechanism. Proof that histamine is released by sensitized tissues when they are brought in contact with allergen was obtained by Katz and Cohen (1941), who observed a shift of histamine from blood-cells to plasma when the blood of patients suffering from pollen and dust allergies was brought in contact with allergen. This interesting technique has received less attention than it deserves. Various studies have been made of the effect of allergy on the amount of histamine in the venous blood. For example, Rose (1940) stated that there was a fall in the histamine blood-level during an attack of angio-neurotic oedema, while in asthma there was considerable fluctuation of these levels, though the changes did not bear any direct relationship to the onset of the asthmatic attack. Randolph and Rackemann (1941), on the other hand, noted that there was a slight increase in the blood-histamine concentration during the asthmatic attack. Horton, Brown, and Roth (1936) and Rose (1941 *b*) found some increase in the blood-histamine after skin stimulation in cases of dermatographism. Some of the reasons why it is difficult to interpret such results have already been discussed. It is possible that various local effects are due to the release of histamine, but that the quantities released are insufficient to have a detectable effect on the blood-histamine.

wealing, this concentration will not cause itching. It appears that higher concentrations of histamine will cause itching in addition to weal formation (Lewis, 1942). Recent observations by Emmelin and Feldberg (1947) throw some light on this problem. They found that nettle stings contained histamine and acetylcholine in concentrations of 0.1 per cent and 1 per cent respectively. The urticaria of a nettle sting is due to the histamine and the pain due to histamine and acetylcholine acting together. The effect of either injected alone is painless. It seems reasonable to postulate that itching and cutaneous pain are due to the local release of both these substances. In small quantities it is possible that they produce itching and in greater quantities they will certainly produce pain.

It has long been known that histamine-like substances are present in many mammalian tissues, and histamine itself has frequently been isolated in crystalline form from such sources. Reliable quantitative estimates of the amount present can be obtained only by pharmacological methods which will detect and measure concentrations down to one part in 100,000,000, or less. It is possible in various ways to distinguish histamine from allied substances. When adequate special tests are made, such assays give a reliable estimate of the histamine content of tissues (Gaddum, 1948). Barsoum and Gaddum (1935) found that histamine is present in particularly high concentrations in the cells of rabbits' blood, and this fact was confirmed by chemical isolation (Code and Ing, 1937). Human blood contains so little histamine that it can be detected only by pharmacological methods. The method of extraction first described by Barsoum and Gaddum was simplified by Code (1937*a*) whose technique is generally used. Code (1937*b*) obtained evidence that most of the histamine normally present in human blood is in the granulocyte cells, and this conclusion was confirmed by the discovery that the blood-histamine was very much increased in myelogenous leukaemia, but not in lymphatic leukaemia (Code and Macdonald, 1937). Haworth and Macdonald (1937), Rose and Browne (1940), and Randolph and Rackemann (1941) found that the blood-histamine in normal persons was about 45 μgm per litre. The concentration remained remarkably constant in any one individual, but this was presumably only a reflection of the fact that under constant conditions the granulocytes remained constant. Thus intracellular histamine cannot have any action on the body unless it is released, and estimates of the total blood-histamine must always be interpreted with caution. Estimations of the plasma-histamine are more likely to give an indication of the effect that the blood will have on the tissues which it reaches, but such estimations are apt to be unreliable because the concentrations are very low. In any case, attempts to demonstrate the release of histamine by following its concentration in the general circulation are liable to fail because any histamine which is released into the blood is likely to be absorbed again before it reaches the veins after circulating once round the body. In an experiment by Adam and Hunter (1948), 5,000 μgm of histamine were infused intravenously in a man over a period of four hours. This procedure produced marked flushing, tachycardia, hypotension, and vomiting, but the drug dis-

In attempts to produce antihistamine drugs of greater potency and less toxicity numerous new derivatives of these compounds and several unrelated compounds have been studied recently, to which brief reference must be made. Antistan (Meier and Bucher, 1946) is closely related to Antergan, but the dimethylamino linkage is replaced by an imidazole ring (Fig 2), while Hetramine (Feinstone, Williams, and Rubin, 1946) is the pyrimidine analogue of

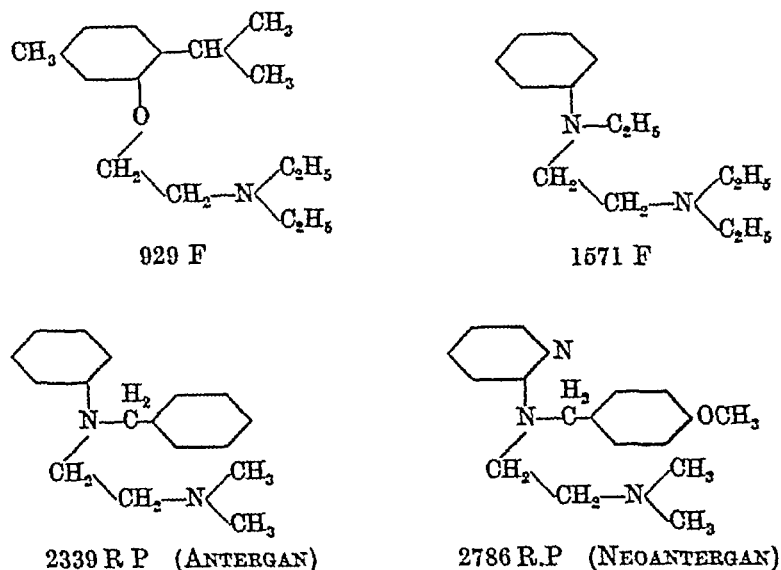


FIG 1

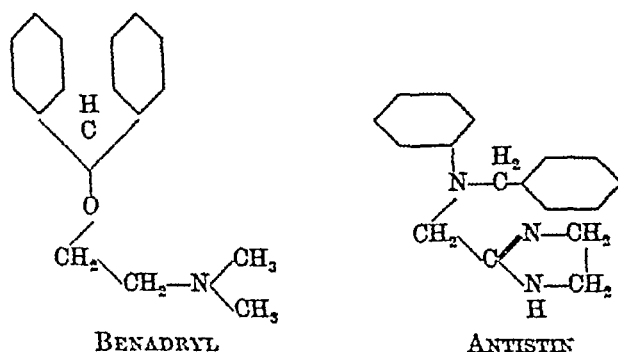


FIG 2

Pyribenzamine A further series of compounds are derivatives of Anthisan. Weston (1947) replaced the methoxy benzyl group of Anthisan by a thiophenyl group. Two derivatives of this compound have been investigated by Litchfield, Adams, Goddard, Jaeger, and Alonso (1947). They are halogen derivatives and have been named Chlorothen and Bromothen. These substances, α -naphthylmethyl ethyl-b-chlorethylamine and b-2-biphenyloxy-ethyl-b-chlorethylamine, have been shown by Achenbach and Loew (1947) to be of considerable pharmacological interest. As well as being potent antagonists of histamine they

Summary The evidence is now conclusive that histamine plays a part in the manifestations of anaphylaxis in animals. There is not, however, absolute proof to support the theory that histamine plays a part in human allergy, though there is, as has been shown, very considerable circumstantial evidence to this effect.

Pharmacology of Antihistamine Drugs

In 1937, Staub and Bovet reported that thymoxy-ethyl-diethylamine, labelled 929 F in their series, would prevent anaphylactic shock in guinea-pigs, and Chimenko, Homburger, and Messer (1941) found that it would protect guinea pigs from two lethal doses of histamine administered parenterally. The antihistamine effects of the drug were also confirmed by Rosenthal and Brown (1940), and Rosenthal and Minard (1939) had shown that it had a local anaesthetic action. Because of its toxicity, however, no attempt was made to use it clinically. In 1939, Staub reported her results with another series of Fourneau compounds containing an ethylene-diamine radicle. The most effective of the substances studied was labelled 1571 F which she found to have antihistamine and anti-anaphylactic properties, though it had no effect on histamine skin reactions. Wilcox and Seegal (1942) showed that this compound could protect guinea-pigs against two to six times the lethal dose of histamine, though it produced toxic effects in the animals. After a short clinical trial its use was abandoned because of its toxicity.

Halpern (1942), after studying a large number of compounds, selected two, labelled 2325 R P and 2339 R P, as being the most effective. Fig 1 shows the chemical formulae of some of these earlier compounds. The compound 2325 R P differs from 1571 F only in the substitution of a dimethyl for a diethyl group, while 2339 R P differs from 2325 R P only in the substitution of a benzyl for an ethyl group. Halpern found that 2339 R P was a specific antihistamine 15 times more potent than 2325 R P and 150 times more potent than 1571 F. This drug (2339 R P) was introduced for clinical use in 1942 in France under the trade name Antergan, but because of the chaotic state of Europe at that time Halpern's discoveries did not become generally known till 1945, by which time Bovet, Horelois, and Fournel (1944) had produced an even more potent, more specific, and less toxic antihistamine drug known as 2786 R P (Neoantergan). This drug, now sold in this country under the proprietary name of Anthusan, differed from Antergan in the replacement of a benzene by a pyridine group and the addition of a methoxy group to the benzyl ring (Fig 1). It will be referred to subsequently as Anthusan. In the following year two antihistamine drugs were produced in America, Pyribenzamine (Mayer, Hutterer, and Scholz, 1945) and Benadryl (Loew, Kaiser, and Moore, 1945). Both have been widely used therapeutically in America. Benadryl is the only antihistamine drug which has been in general clinical use in this country during the last two years. Pyribenzamine differs from Anthusan in the absence of the methoxy group on the benzyl ring, and Benadryl is a benzhydryl ether (Fig 2).

(1946) to have a quinidine-like action on the rabbit's auricle. Our studies in human subjects, however, have failed to demonstrate this effect (Hunter, 1947). By virtue of their local anaesthetic, quinidine-like, and anti-acetylcholine effects, antihistamine drugs belong to a large group of substances which have these actions in common. This group includes spasmolytics like Trasentan, analgesics like Pethidine, local anaesthetics like procaine, and atropine-like substances. The common properties of all these drugs suggest that their site of action must be a similar one or that they are adsorbed on to more than one of the components of reactive tissue. This subject has been reviewed by Burn (1948).

A drug may prevent histamine from producing its pharmacological action in several ways—it may prevent the release of histamine from the tissues, it may diminish or abolish the action of histamine by direct combination with it, it may act by indirect physiological antagonism by producing reactions directly opposed to that of histamine, or it may block the action of histamine by uniting with its tissue receptors. Antihistamine drugs exert a profound effect in preventing the action of injected histamine, but there is little evidence to suggest that they prevent its release by the tissues. If this were so, they would prevent the stimulation of gastric secretion by histamine, which as we shall see does not occur. It is repeatedly stated that antihistamine drugs do not act by combining with histamine, destroying it, or rendering it inactive. It must be confessed, however, that the only evidence which exists to this effect concerns 929 F (Staub, 1939). It is unlikely that antihistamines act by indirect physiological antagonism. Till recently it seemed theoretically possible that they might act by potentiating the effect of adrenaline. This theory, as we have seen, became untenable when drugs with a potent antihistamine action were discovered which also had powerful sympatholytic properties. All the available evidence suggests that these drugs antagonize histamine by being taken up by the tissue receptors thereby blocking the normal pharmacological responses of histamine (Wells, Morris, Bull, and Dragstedt, 1945, Halpern and Mauric, 1946, Gaddum, 1948). Additional evidence that histamine is concerned in the manifestations of anaphylaxis in animals has resulted from the use of antihistamine drugs, which will abolish or significantly modify anaphylactic responses due to histamine. This subject has been recently reviewed by Loew (1947).

In contrast to the effect which these drugs have in preventing the spasm of smooth muscle and the vasodilator action of histamine in animals, they do not significantly interfere with the normal secretion of gastric hydrochloric acid or its increased production after the injection of histamine (Friesen, Baronofsky, and Wangenstein, 1946, Sangster, Grossman, and Ivy, 1946). Significantly, too, antihistamine drugs have failed to influence materially the toxic effects resulting from the administration of trypsin (Wells, Morris, and Dragstedt, 1946b).

There is some evidence that antihistamine drugs are less active against anaphylactic shock than against histamine shock (Arbesman, Koepf, and

antagonize the action of adrenaline Thephorn (1504 N U) (Lehmann, Hagan, Barbarow, and Roe, 1947) has also been shown to have sympatholytic properties Another compound, 3277 R P, first studied by Halpern (1946), is a phenothiazine derivative of Anthusan At the time of writing these preparations have received only scant clinical trial The drugs detailed above vary in their antihistamine properties, and none of them are absolute specifics in this respect In addition to their antihistamine effects they have in varying degree anti-acetylcholine, local anaesthetic, sympathomimetic, or sympatholytic actions Antispasmodic and quinidine-like properties have also been shown by some members of this group (Dews and Graham, 1946, Sherrod, Loew, and Schloemer, 1947) Consideration of their varying properties is necessary in order to understand the probable action of these drugs Careful comparative antihistamine studies have been conducted by a number of workers, among them Schuld (1939), Friedlaender, Feinberg, and Feinberg (1947), Winter (1947), Graham (1947), March and Davis (1947), and Reuse (1948) Though their experiments were not all conducted in the same manner there is general agreement in their results, and there is now little doubt that Anthusan is the most potent and specific antihistamine drug with the least anti-acetylcholine action Other drugs, including Benadryl and Antistin, have a considerable anti-acetylcholine action as well as antihistamine effects

The local anaesthetic effects of antihistamine drugs have not as yet been fully investigated Graham (1947) suggested that there is a relationship between the potency of the drug as a local anaesthetic and its potency as an antihistamine He found that Anthusan, Benadryl, and Antistin were respectively 3.3, 2.5, and 1.5 times as potent as procaine Reuse's (1948) findings, on the other hand, suggest that the relationship is between the anti-acetylcholine and the local anaesthetic effects of the drugs Leavitt and Code (1947) have shown that the local anaesthetic effect of the drugs wears off in approximately an hour, and that after that time comparative antihistamine studies can be carried out It is significant that they then found that Anthusan produced the greatest reduction in the histamine wheel

Benadryl, Anthusan, and Pyribenzamine have been shown to potentiate the action of adrenaline (Loew, MacMillan, and Kaiser, 1946, Yonkman, Chess, Hays, Rennick, and Mayer, 1946, Sherrod, Loew, and Schloemer, 1947) This effect has been demonstrated only in biological preparations, and not in the unanaesthetized animal or man On the other hand, the more recent drugs described by Achenbach and Loew (1947) antagonize the action of adrenaline, as does 929 F Therefore, as some potent antihistamines potentiate and others antagonize adrenaline, it is difficult to believe that there can be any relationship between their adrenaline and antihistamine effects, and it is now generally considered that no such relationship exists (Loew, 1947) Remstein and McGavack (1946) failed to elevate the blood-sugar concentration in man by the administration of Benadryl or Anthusan, though McGavack, Elias, and Boyd (1947) observed increased glucose tolerance after the intravenous administration of Benadryl in man Anthusan was shown by Dews and Graham

offers an explanation of the effects on the skin histamine reaction of the oral administration of the drugs even when no anaesthetic action is detectable

Last and Loew (1947) have demonstrated that whereas antihistamine drugs have a marked influence on the increased capillary permeability which follows intradermal injections of histamine, Benadryl produces little effect on the weal resultant on the injection of horse serum, trypsin, or staphylococcal toxin in sensitized animals. This led the authors to the conclusion that histamine does not play a predominant role in the increased permeability which accompanies the antigen antibody reaction. The work of Drewsbach (1947) confirms these findings because in experimental skin-sensitization to penicillin and horse serum he was unable to prevent the development of the Arthus type of skin sensitivity reaction by the administration of Benadryl or Pyribenzamine.

Hunter and Hill (1947) have studied the wealing phenomena which result from the intradermal injection of liver in the sensitized person and have noted a considerable reduction in threshold after the oral administration of Anthusan. Arbesman, Koepf, and Lenzner (1946) demonstrated the reduction of the response to injected ragweed antigen, but Friedlaender, Feinberg, and Feinberg (1946) found that though the local application of Benadryl had a modifying effect, there was no practical interference with the antigen-antibody weal when the drug was given by mouth. The practical point of importance which emerges is that skin testing should not be carried out in patients who have recently ingested an antihistamine drug.

Curry (1946) showed that by administering Benadryl intravenously he could protect asthmatics from the bronchospasm produced experimentally by histamine. Feinberg (1948) has reported similar results. That this form of artificially induced bronchospasm may bear little relationship to naturally occurring asthma is suggested by the findings of Levy and Seabury (1947), who were unable to show by spirometric studies any consistent improvement in the vital capacity of asthmatics when Benadryl was administered.

Antihistamine drugs will prevent the effects of parenterally administered histamine, but there are no reported studies which estimate accurately the amount of drug required to antagonize a known amount of histamine, nor, at the time of writing, are there any reports of the relative protective effect of these drugs. At present, antihistamines are graded as to their potency and comparative activity by their capacity to protect animals against lethal doses of histamine. It is, however, manifestly unwise to compare and assess the therapeutic efficacy of the various drugs by standards based entirely on animal experiments, and comparative studies in man are desirable. The information which is required is the amount of histamine which will be combated by the maximum dose of each drug which can be tolerated by man.

McElin and Horton (1945) suggested that the administration of Benadryl might possibly modify the gastric acidity. This preliminary work, however, has not been confirmed. Doran (1947), reporting his studies on the effect of Benadryl on gastric acidity, suggested that in cases of active duodenal ulcer there was an increased secretion of hydrochloric acid. McGavack, Elias, and

Lenzner, 1946, Wells, Morris, and Dragstedt, 1946*a, b*) As has been pointed out by Loew (1947), this may be due to the fact that histamine is released in intimate contact with the effector cells and does not prove that histamine is not largely concerned in producing the symptoms of anaphylaxis

Summary. The pharmacology of antihistamine drugs has been reviewed Anthusan has been shown to be the most potent and specific member of the group They all protect animals against histamine shock and significantly modify the anaphylactic response, but have no effect on the histamine-induced flow of gastric hydrochloric acid All the drugs are powerful local anaesthetics and have in varying degree an anti-acetylcholine effect, while some have been shown to have a quindino-like action Some have a sympatholytic action, but the majority of the drugs in clinical use potentiate the action of adrenaline in biological preparations, though this property has not been demonstrated in man

Experimental Studies with Antihistamine Drugs in Man

A considerable literature is devoted to the effects of oral and local administration of antihistamine drugs in modifying the weal and flare reaction to histamine and the antigen-antibody response in the human skin (Ehas and McGavack, 1946, Friedlaender, Feinberg, and Feinberg, 1946, Arbesman, Koepf, and Lenzner, 1946, Aaron and Abramson, 1947, Cohen, Friedman, Zonis, Burke, and Abram, 1947, Hunter and Hill, 1947, Code, Keating, and Leavitt, 1948) There is general agreement that antihistamine drugs modify the size of both the weal and flare due to the injection of histamine, an effect which is particularly striking when the drugs are injected locally The majority of the papers which deal with the effect of locally injected antihistamine in modifying the histamine response are open to criticism because no consideration has been taken of the local anaesthetic properties of the drugs, for, as shown by Lewis (1927), local anaesthetics considerably modify the weal and flare response to histamine When the drugs are given by mouth, there is no detectable anaesthesia of the skin, and, though possible, it is improbable that their flare-reducing properties when administered orally are due to their anaesthetic action Impulses normally initiated by the histamine injection and carried antidromically to the blood-vessels in the flare region are interrupted or not initiated when an antihistamine drug is present, and this effect persists after the anaesthetic effect has worn off (Code, Keating, and Leavitt, 1948) In comparing the local anaesthetic actions of Benadryl, Anthusan, Pyribenzamine, 3277, and 3015, these authors noted that the last two drugs were the most potent This order of potency was the exact reverse of their flare-reducing action They therefore decided that the flare-reducing effect of antihistamine drugs is not dependent on their local anaesthetic effects They pointed out that the antihistamine and local anaesthetic effects may be the result of differences of degree of action on nervous tissue rather than separate actions on different tissues, the concentration of the drug required to block the flare response being considerably less than that required to produce anaesthesia This conception

and is the route of choice in anaphylactic emergencies in man. We would add a word of caution that this method of administration has not been widely used as yet and is not without danger, we have had one alarming case of collapse after the parenteral use of Anthusan, and as these drugs are so quickly absorbed the oral route is usually satisfactory in practice.

Local application There is undoubtedly a place for the local application of antihistamine drugs in a suitable base in the itching dermatoses. Feinberg and Bernstein (1947) have used this method with success. For local application to the nasal mucous membrane Antistin is the drug of choice as it is very much less irritating than the other drugs. We have found that local application to the nose has been occasionally successful in rhinitis when the oral administration of these drugs has failed.

Duration of treatment As antihistamine drugs do not prevent the production of histamine, but act by blocking the tissue receptors for histamine, it is apparent that the underlying allergic or anaphylactic tendency persists in spite of the drug, and therefore administration of the antihistamine has to be continued either indefinitely in a few cases or at least till the allergic or anaphylactic tendency has subsided spontaneously or as the result of artificial or natural desensitization. Thus, the use of these drugs in no way absolves the physician from the responsibility of seeking for and eliminating an offending allergen, or from attempting specific desensitization treatment if that be possible and desirable.

Side effects A single dose of 100 mg of Benadryl will cause side effects in over 50 per cent of cases (Feinberg, 1946) and the incidence of unpleasant reactions is probably as frequent with Antistin, though Britton (1947) claims the incidence to be only 37 per cent. With a daily dose of 600 mg of Pyribenzamine the incidence of side effects is between 20 and 30 per cent (Feinberg, 1946, Arbesman, Koepf, and Lenzner, 1946). In about 200 cases treated by us with Anthusan in daily doses of between 0.6 and 0.8 gm, 37 per cent of patients complained of side effects when the drug was first administered, but in only 23 per cent did these persist after the first 48 hours of treatment. The practical superiority of Anthusan and Pyribenzamine over Benadryl lies in the fact that they are not only more active weight for weight, but can be tolerated in much larger doses and so may benefit some patients for whom the necessarily smaller dose of Benadryl may have proved ineffective.

The Table shows that the principal side effects of all antihistamine drugs are sleepiness and fatigue. These symptoms may to begin with be very pronounced so that the drugs should never be given initially to any person about to perform work requiring skilled judgement, such as driving a motor-car. There are two methods whereby this hypnotic effect may be minimized. One is to give small doses initially and then gradually to increase the quantity till at the end of three or four days the full therapeutic dose is reached, in this way the patient becomes tolerant to the hypnotic effect, and the tendency to sleepiness usually wears off more or less completely. Alternatively, amphetamine may be given, a dose of 5 mg in the morning and possibly repeated at midday will minimize

Boyd (1947), on the other hand, claimed that after administration of full doses of Benadryl for three or four weeks there is some diminution in the flow of hydrochloric acid. It is interesting to note, however, that in one of their cases there was a decided increase in gastric acidity when the drug was administered, though in the majority there was a diminution. If the profound sedative effect of Benadryl and its atropine-like and spasmolytic actions are considered, it would not be surprising if it caused some reduction in gastric secretion quite apart from its antihistamine effect. Anthisan and Pyribenzamine have not proved themselves to be of value in causing diminution of gastric secretion and none of the drugs significantly alter the histamine-induced flow of gastric hydrochloric acid (Decourt, Rmieri, and Sonnet, 1945, Sangster, Grossman, and Ivy, 1946).

Summary Experimental antihistamine work in man has been mainly confined to a consideration of the effect of these drugs on the histamine and antibody and antigen whealing phenomena. Because of their effect in reducing the flare which results from the intracutaneous injection of histamine it is evident that they prevent the axon reflex by a direct action on nervous tissue in the skin. Sufficient intravenous antihistamine studies have been conducted to prove how dramatically the drugs abolish the effects of parenterally administered histamine. They have also been shown to prevent histamine-induced bronchospasm in asthmatics, but they have proved disappointing in abolishing naturally occurring bronchospasm. In human as in animal experiments they have not been found to influence the histamine-induced flow of gastric hydrochloric acid or to have a significant effect on normal gastric secretion.

Mode of Administration, Dosage, and Side Effects

Dosage Benadryl and Pyribenzamine are usually prescribed in doses of 50 mg and Anthisan and Antistin in doses of 100 mg. The maximum daily dose of Benadryl is about 400 mg, Pyribenzamine, 600 mg, and Antistin and Anthisan, 800 mg. Higher doses of all these drugs have been given, and as far as is known the only limiting factor is the production of side effects. The drugs are quickly absorbed and fairly quickly excreted in the urine, so that the effect of a single dose lasts only from four to six hours. It is thus apparent that they must be administered three times a day, and in some subjects it is necessary to give an additional dose as late as possible at night so as to 'cover' the hours of sleep, for it is not unusual, when only three doses are given, for a recrudescence of the allergic tendency to occur in the early morning when the effect of the last dose has worn off. Children tolerate the drugs well and over the age of 12 years can be given the same dosage as adults with appropriately smaller doses under that age. As the drugs have an unpleasant taste and as they are powerful local anaesthetics, the tablets or cachets should be swallowed whole and not chewed. Benadryl is prepared for intravenous use in a purified solution containing 10 mg per c.c. The parenteral method of administration has been recommended in status asthmaticus (Waldbott, 1947),

Therapeutic Applications

Urticaria and angioneurotic oedema The dramatically beneficial effects of Antergan in the treatment of urticaria were first demonstrated by Gaté, Thiers, Cuilleret, and Pellerat (1942) Since then it has been repeatedly shown that all the antihistamine drugs in clinical use—Benadryl (O'Leary and Farber, 1945, Waldbott, 1946, Eyermann, 1946, Lynch, 1947), Anthusan (Pellerat, 1946, Gaté and Pellerat, 1947, Hunter, 1947), Pyribenzamine (Arbesman,

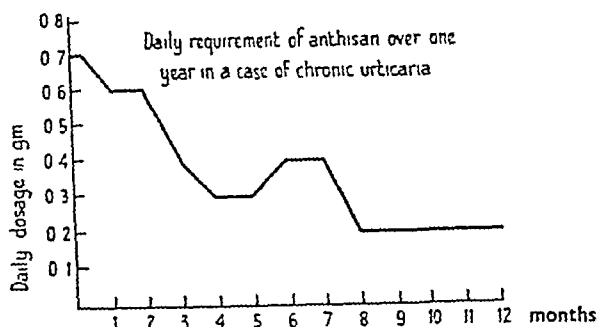


FIG 3

Koepf, and Lenzner, 1946, Feinberg, 1946), and Antistan (Britton, 1947)—are valuable in the symptomatic treatment of this condition. Antistan seems to be the least effective (Britton, 1947), but there is probably no great difference in the respective efficacy of the other drugs, though Pyribenzamine and Anthusan being better tolerated can be given in larger doses. Occasionally, a patient refractory to one drug of the series will respond satisfactorily to another. As might be expected from the mode of action of antihistamine drugs, though they will prevent new lesions from occurring, they have little or no effect on established urticarial lesions. These usually subside spontaneously, but in emergencies such as swelling of the tongue or oedema of the glottis, treatment with adrenaline is necessary. The first obvious therapeutic effect of antihistamines in urticaria is diminution of the skin irritation, which occurs within half an hour of the first dose being taken. This is followed by a decrease in the number of lesions appearing. Initially, a small dose of the drug should be given three times a day. The size of the dose can be gradually increased, if full control is not at once established, till an optimum effect is procured. After all lesions have been abolished for some days the dose can be gradually reduced, to be increased again on any sign of recrudescence of the disorder. Occasionally the underlying allergic tendency persists and it may be necessary to go on giving the antihistamine for long periods. We have had a few patients who have been taking Anthusan for two years. In all of them a smaller dose of Anthusan now keeps the urticaria in check than was necessary at the beginning of treatment, showing that tolerance to antihistamines does not develop and suggesting that the allergic tendency in these cases is gradually subsiding (Fig 3). Antihistamine treatment should never be terminated suddenly, as

the drowsy feeling and after a few days its administration can be stopped in the majority of cases. Because of the soporific effects of antihistamines, care has to be taken in the coincident administration of hypnotics and sedatives. On the other hand, the drugs occasionally produce a curious feeling of nervousness and tension leading to insomnia.

Anthusan and Pyribenzamine have both been shown to produce increased motility of the bowel in animals, whereas Benadryl has an antispasmodic action.

Side Effects

<i>Benadryl</i> (Feinberg, 1946)	<i>Pyribenzamine</i> (Arbesman, Kopf, and Lenzner, 1946)	<i>Anthusan</i> (Hunter and Dunlop, 1947)
Drowsiness and fatigue	Drowsiness and fatigue	Transient drowsiness
Dizziness	Nausea	Persistent drowsiness and fatigue
Dryness of the mouth	Dizziness	Nausea
Nausea	Headache	Dizziness
Insomnia and nervousness	Dryness of the mouth	Dryness of the mouth
Headache	Vomiting	Diarrhoea
Asthma	Palpitation	Feeling of unreality and tension
	Nervousness	Headache
	Diarrhoea	Asthma
	Insomnia	Vomiting
	Toxic rash	Dysuria
		Toxic rash

(Sherrod, Loew, and Schloemer, 1947) This probably accounts for the greater frequency of nausea and vomiting when Anthusan and Pyribenzamine are used than is the case with Benadryl. Such side effects, however, can usually be avoided by taking the drugs after meals and not on an empty stomach. Benadryl, having a strong atropine-like action, commonly produces dryness of the mouth, and atropine and its congeners should never be prescribed with it. There is, however, no contra-indication to the coincident use of sympathomimetic drugs with antihistamines. In fact their administration may be a valuable adjuvant to treatment when cases are only partially controlled by antihistamine drugs.

Toxic effects, sufficiently severe to necessitate discontinuance of antihistamines, are encountered only in about five per cent of cases. A patient who experiences toxic effects as the result of one drug will usually experience them with others of the series, but this is not always the case, and a trial should be made of alternative drugs before the use of these preparations is finally abandoned. In our experience patients are much more tolerant to Anthusan than to Benadryl, but occasionally the reverse is true. In the five years of their use no deaths or toxic effects leading to organic change have been reported from the therapeutic use of antihistamine drugs, nor does increased tolerance occur even after prolonged administration.

Summary The dosage, mode of administration, and side effects of antihistamine drugs have been described. Methods of minimizing side effects have been suggested. There is an absence of serious toxic reactions, and increased tolerance does not occur.

protection of Anthisan with a marked diminution or complete absence of reaction. They showed that desensitization to liver could be undertaken with much greater safety if the patient were given the antihistamine in adequate doses for 24 hours prior to the procedure. In very severe cases, however, showing skin sensitivity to a dilution of liver-extract of 1 in 100,000 or more, adrenaline should always be used along with each desensitizing dose of liver-extract in addition to the antihistamine treatment. More recent work by Hill (1948) suggests that a scheme of 'tapered' dosage with Anthisan can take the place of desensitization in all but the most sensitive cases. Before an injection of liver is given to a liver-sensitive patient 1.3 gm. of Anthisan is given in divided doses during the 24 hours prior to the injection. Thereafter, if there is no reaction to the liver the 24-hour course of Anthisan prior to each fortnightly liver injection is reduced by 200 mg. till on the eighth occasion the liver is given without any covering course of antihistamine at all. If, however, any reaction to the liver does occur at any stage, the previous dosage with Anthisan is maintained for two further injections.

Insulin sensitivity Generalized urticarial reactions to insulin are rare, but occasionally occur, specially when a patient starts to take insulin for a second time after the lapse of an interval in which no insulin has been given. That such reactions may be considerably modified by antihistamine therapy has been demonstrated by Hunter and Hill (1947) and Leavitt and Gastineau (1947). Treatment with antihistamines has seldom to be given to insulin-sensitive cases for more than a week or so, by which time spontaneous desensitization may be confidently expected. Local reactions are also considerably benefited.

Asthma Reference has already been made to the action of antihistamine drugs in the prevention of the experimental bronchospasm induced by histamine in human asthmatic subjects (Curry, 1946). This finding encouraged the hope that they might be effective in the prevention and treatment of the asthmatic state. In early therapeutic studies with Antergan, Gaté, Thiers, Culleret, and Pellerat (1942) and Sciclounoff and Junet (1943) obtained conflicting results. Using Anthisan, Pellerat (1946) stated that 45 per cent. of cases were improved, but Feinberg (1946) reported that not more than one patient in five derived any benefit from the drug. Benadryl and Pyribenzamine have now been used extensively in the treatment of asthma, but reports on their usefulness in this condition are also conflicting. Using Benadryl, Levin (1946) and Waldbott (1946) claimed benefit in 65 and 30 per cent. of cases respectively, while Koelsche, Prickman, and Carryer (1946) had good results in cases of asthma associated with hay fever. Using Pyribenzamine, Arbesman, Koepf, and Lenzner (1946) and Feinberg (1946) reported improvement respectively in 50 and 28 per cent. of cases treated. In a review of the clinical use of antihistamine drugs Waldbott (1947) stated that in 40 to 50 per cent. of asthmatic cases the number of attacks is reduced by their oral administration, and that the attack itself is relieved in 65 to 75 per cent. of cases by their intravenous administration. We (Hunter and Dunlop, 1948) have not been able to confirm these results. In a prolonged observation of a series of asthmatic patients treated

this may precipitate a recrudescence of lesions more violent than before treatment. This rebound phenomenon has also been noted in the weal and flare response to histamine in the human skin on stopping the antihistamine drug.

Pruritus Just as prompt relief from itching occurs with antihistamine treatment in urticaria and angioneurotic oedema, so these drugs may ameliorate itching in pruritus due to many other causes. In acute and chronic atopic dermatitis Friedlaender, Feinberg, and Feinberg (1946) noted relief from itching after their administration in 20 out of 25 cases, and Waldbott (1946) and Walton and Kristjansson-MacDonell (1947) had similar results. The drugs have no effect on the skin lesion itself, but the patient ceases to scratch, with resulting improvement. Hunter and Dunlop (1947) reported the value of antihistamines in the control of the pruritus of obstructive jaundice, and Friedlaender, Feinberg, and Feinberg (1946) and Lynch (1947) noted pronounced relief after their use in cases of pruritus vulvae and ani. Baer, Sulzberger, and Witten (1947), however, in a study of several hundred cases found that a strong antipruritic effect was exerted by antihistamines in only 10 per cent of itching dermatoses, excluding urticaria.

Allergic reactions to drugs The work of Landsteiner and Chase (1941), among others, makes it clear that certain drugs by combining with body proteins form antigenic compounds which may lead to the production of hypersensitiveness. In most instances the occurrence of an idiosyncrasy to the drug is the only evidence that such a state of affairs exists. Untoward reactions occur with drugs such as acetylsalicylic acid, sulphonamides, and penicillin, in which the reactions are obviously allergic in type, but it must be borne in mind that there are other types of idiosyncrasy in which there is no proof that the reaction is an allergic one. The criteria designed to distinguish between these reactions have been suggested by Dragstedt (1947) and the introduction of antihistamine drugs has given us a diagnostic weapon which will aid in their differentiation. It is becoming evident that the majority of acute urticarial manifestations, whatever their cause, are influenced or modified by antihistamine drugs, but there remains a large group of toxic reactions in which, as has been mentioned above, there is no real evidence of allergy. The fact that histamine is not a major factor in their production is confirmed by their lack of response to antihistamine drugs.

Serum sickness It is generally agreed that though the urticaria and pruritus may be dramatically abolished by antihistamine drugs, the condition is not completely controlled. Joint pains are resistant to treatment, so analgesics should be administered, and splinting may be required. Though the pyrexial reaction may be modified, the course of the disease is not shortened and drug therapy has to be continued until the allergic state has spontaneously subsided.

Liver sensitivity Arbesman, Koepf, and Lenzner (1946) first reported that injections of liver-extract could be given to a liver-sensitive patient without a reaction while he was taking an antihistamine drug. Walton and Kristjansson-MacDonell (1947) had a similar case, while Hunter and Hill (1947) reported nine patients with liver-sensitivity who could be given injections of liver under the

protection of Anthisan with a marked diminution or complete absence of reaction. They showed that desensitization to liver could be undertaken with much greater safety if the patient were given the antihistamine in adequate doses for 24 hours prior to the procedure. In very severe cases, however, showing skin sensitivity to a dilution of liver-extract of 1 in 100,000 or more, adrenaline should always be used along with each desensitizing dose of liver-extract in addition to the antihistamine treatment. More recent work by Hill (1948) suggests that a scheme of 'tapered' dosage with Anthisan can take the place of desensitization in all but the most sensitive cases. Before an injection of liver is given to a liver-sensitive patient 1.3 gm. of Anthisan is given in divided doses during the 24 hours prior to the injection. Thereafter, if there is no reaction to the liver the 24-hour course of Anthisan prior to each fortnightly liver injection is reduced by 200 mg. till on the eighth occasion the liver is given without any covering course of antihistamine at all. If, however, any reaction to the liver does occur at any stage, the previous dosage with Anthisan is maintained for two further injections.

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alternately with Anthusan and dummy control tablets, no improvement was found as the result of Anthusan therapy which could not be attributed to chance. The difficulties in the therapeutic assessment of any drug or form of treatment in asthma are notorious. The spontaneous fluctuations which occur in the severity and frequency of the attacks and the suggestibility of its sufferers to any form of treatment, especially if it is new and administered with impressive gravity, has made asthma the happy hunting ground for the uncritical therapeutic enthusiast. Much of the work claiming antihistamines to be of therapeutic value in asthma is insufficiently controlled, and in our view there is inadequate evidence to justify their use in the treatment of the condition.

Hay fever In contrast to the conflicting results obtained with antihistamines in the treatment of asthma, all observers are agreed as to the efficacy of these drugs in hay fever. Levin (1946), Feinberg (1946), and Waldbott (1947) have reported good results using Benadryl. Arbesman, Koepf, and Lenzner (1946) found that 85 per cent of their patients receiving Pyribenzamine were benefited and Arbesman, Cohen, and Osgood (1947) claimed that combined Pyribenzamine and desensitization therapy gave relief in 95 per cent of cases. Over 75 per cent of our patients given Anthusan were greatly improved, and favourable results were also reported by Britton (1947) using Antistin. Desensitization treatment in hay fever is uncertain in its effects, not entirely free from risk, and laborious to carry out. In comparison the symptomatic control of hay fever by antihistamines is so much more simple and reliable as to make it the treatment of choice in the majority of cases. In very severe or resistant cases, however, the patients may be given antihistamine drugs during the hay fever season after a preliminary course of desensitizing injections. The drugs should not be given during the process of desensitization, since sensitivity reactions may be delayed without being greatly modified in severity.

Perennial rhinitis It appears that Anthusan and Pyribenzamine are more effective in the treatment of this condition than Benadryl. For example, Feinberg (1946) noted improvement in only 15 per cent of patients treated with Benadryl and in 64 per cent of those treated with Pyribenzamine. The same patients who failed to respond to Benadryl were often much improved by Pyribenzamine. It is generally agreed, however, that the benefit derived from antihistamines in perennial rhinitis, though often considerable, is not so dramatic as in hay fever. When nasal sepsis and nasal polypi are found to be present, these conditions should be treated before resorting to the use of antihistamines. A strong psychological factor is often present in the aetiology of perennial rhinitis, as is shown by the considerable symptomatic improvement which occurred in 35 per cent of our cases as the result of administering dummy tablets. The assessment of the therapeutic value of a remedy is, therefore, difficult in this condition, as it is in asthma. Before it can be stated that improvement is due to antihistamine drugs, there must not only be complete relief of symptoms, but a conversion to normal of the typically allergic nasal mucosae seen in these cases. These standards, which included biopsy of the nasal mucous membrane before and after treatment, have recently been applied

by one of us in a clinical study of 40 cases of perennial rhinitis treated with Anthusan. In 45 per cent of the cases there was complete symptomatic relief with reversion of the nasal mucosa to normal. In a further six per cent of cases, occasional sneezing occurred though the mucosa became completely normal. Such are the vagaries of the disorder, however, that two patients with typically allergic nasal mucosa, who were taking only dummy tablets, not only obtained complete symptomatic relief, but showed in addition on biopsy of the nasal mucous membrane objective evidence of cure as well.

Alimentary allergy The use of antihistamine drugs in cases of alimentary allergy has been recommended by Feinberg (1946), and we have noted improvement to follow their use in several patients. Spontaneous desensitization to food may well take place under the protective influence of antihistamines. Until, however, the subject has been investigated more fully, it is impossible to make dogmatic statements as to their efficacy in this condition.

X-ray sickness The mechanism of X-ray sickness is unknown, but it has been thought possible that it may be due partly to the release of physiologically active histamine, the result of tissue injury by the X-rays. This theory is supported to some extent by the fact that symptoms of X-ray sickness bear a similarity to the effects produced by the injection of histamine. Lofstrom and Nurnberger (1946) using Benadryl in the treatment of X-ray sickness claimed that as a result there was considerable amelioration of symptoms in their cases. In their paper no mention is made of the dosage of X-rays employed, the quantities of antihistamine drugs given varied from patient to patient, some of the improvement in symptoms which they claimed to be due to the administration of the drugs could well be attributed to other factors and, lastly, there were no controls. We have recently conducted an experiment to determine whether Anthusan was of value in the prevention of X-ray sickness. All the patients chosen were receiving treatment because of carcinoma of the breast, they were all given standard dosage of X-rays, and every alternate patient was treated with an inactive preparation of similar appearance to the Anthusan tablets. Our results convinced us that in the circumstances of the experiment this particular antihistamine drug, which is among the most potent, was of no value whatsoever in the prevention or treatment of irradiation sickness.

Miscellaneous conditions No benefit has been reported from the administration of antihistamine drugs in allergic purpura. In scleroderma some observers have noted a temporary improvement with increased freedom of movement, but it has not been maintained (O'Leary and Farber, 1947). Two cases of periarteritis nodosa, two of dermatomyositis, and a number of cases of migraine which we have treated were not improved.

Summary Antihistamine drugs produce dramatic relief in acute and chronic urticaria in over 80 per cent of cases. In hay fever they are almost as effective, while in vasomotor rhinitis about 50 per cent of patients derive marked benefit. Antihistamines have a place in the treatment of sensitivity reactions to liver, insulin, penicillin, and sulphonamides, especially when the reactions occurring to these drugs are purely urticarial in type. In serum sickness, though they

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improve the urticaria, they have little or no influence on the arthralgia and pyrexia. Antihistamines are of undoubted value in diminishing itching in some cases of pruritus arising from a variety of causes. The claims put forward for antihistamine drugs in the treatment of asthma are variable and contradictory, and are often based on ill-controlled experiments. In our view they have no place in the treatment of asthma. Nor has their value been proved in X-ray sickness, allergic purpura, scleroderma, migraine, periarteritis nodosa, or dermatomyositis.

It appears that antihistamine drugs have their main sphere of usefulness in the treatment of conditions characterized by vascular phenomena in the skin and mucous membranes bearing a resemblance to the effects of locally applied histamine. It is significant that in the bronchospasm of asthma, in the arthralgia of serum sickness, and in other 'deep seated' allergic states these drugs have not proved themselves to be of value. Possible reasons for this are that in these allergies the histamine is released in intimate contact with the effector cell so that it is not clinically possible to produce a high enough local concentration of the antihistamine drug to block the histamine receptors, or histamine may not play a major part in their production.

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THE AETIOLOGY OF CONSTRICTIVE PERICARDITIS, WITH SPECIAL REFERENCE TO TUBERCULOUS PERICARDITIS, TOGETHER WITH A NOTE ON POLYSEROSITIS¹

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With Plates 22 to 24

Introduction

DURING the late war of 1939-45 the close proximity of a large general medical service and a thoracic surgical unit presented us with an unusual number of patients suitable for the clinical study of thoracic disease. The present paper takes the aetiology of constrictive pericarditis as its main theme. It presents, firstly, the clinical picture of constrictive pericarditis and the effect on it of pericardectomy, and secondly, an account of the clinical manifestations and after-history of tuberculous and septic pericarditis, the two lesions which may conceivably precede the constrictive form. These two avenues of inquiry both lead to the conclusion that tuberculosis is the chief cause of constrictive pericarditis, at least in this country. Finally, an attempt is made to clarify two questions that are imperfectly presented in current text-books of cardiology and general medicine, those of adherent pericardium and of polyserositis, questions that are inseparable from the main theme of the paper.

Constrictive Pericarditis

Cases of constrictive pericarditis were described by Lower (1669), Chevers (1842), Wilks (1870), and Broadbent (1895). Pick (1896) recognized the similarity of the clinical picture to that of cirrhosis of the liver. It was Volhard who first showed that the condition could be diagnosed during life on the association of its symptoms with venous congestion in the neck and an unenlarged and poorly pulsating heart, and it is to Volhard and Schmieden (1923) that we chiefly owe the knowledge that the condition can be relieved or cured by pericardial resection. Since then many papers have elaborated the clinical features, indications for, and results of, surgery (Beck, 1931, 1934, 1937, Blalock and Burwell, 1941, Churchill, 1929, Sellors, 1946, White, 1935).

Clinical features The clinical features of our 11 cases of constrictive pericarditis are summarized in Table I. Six were male and five female, and aged

¹ Received June 24, 1948

TABLE I
Clinical Features of Chronic Constrictive Pericarditis Cases

Case number	1	2	3	4	5	6	7	8	9	10	11
Sex and age at first examination	F 20	M 62	M 48	F 63	M 40	F 46	F 56	M 52	M 52	F 18	M 43
Past illnesses and age	Bronchitis 14	None	Jaundice 27 and 30	Pleurisy 37	Haemoptysis 15	Pleural effusion 13	Pleurisy 39	Haemoptysis 43	None	None	Empyema 30
Early symptoms and age at onset	Ascites 17	Dyspnoea 61	Dyspnoea 45	Swollen legs and abdomen 54	Dyspnoea 45	Dyspnoea 31 and 42 Ascites 45	Dyspnoea, swollen legs and abdomen 55	Dyspnoea 48 Oedema 49	Dyspnoea, swollen legs and abdomen 51	Ascites 16	Swollen legs 30 and 33
Mode of onset	Gradual	Sudden	Gradual	Gradual	Sudden	Gradual	Gradual	Gradual	Sudden	Gradual	Gradual
Alive or dead	A	F A	A	D	D	A	D	D	A	A	A
Venous pressure (cm. water)	10	16*	18*	8	5	15	13	10	18*	12	15
Liver enlargement	+	+	+	+	+	+	+	+	+	+	+
Ascites	+	+	+	+	0	+	+	+	+	+	+
Pleural effusion	0	R	0	0	0	0	R	R and L	R	R	0
Oedema	+	0	0	+	0	0	+	+	+	+	+
Arterial pressure	130/80	—	120/74	120/85	125/80	108/90	140/100	110/85	115/90	90/70	140/85
Cardiac irregularity	0	A, F	Ex	Ex	A, F	0	0	A, F	0	0	0
Cardio-thoracic index†	44	—	50	50	48	52	52	55	48	50	47
Diminished cardiac pulsation (X ray)	+	+	+	+	0	0	+	+	—	+	—
Pericardial calcification (X ray)	+	+	+	+	+	0	+	+	0	+	0

† Transverse diameter of heart
 Transverse diameter of chest × 100

A, F Auricular fibrillation
 + Sign present.

Ex Extrasystoles
 0 Sign absent

* By direct measurement.
 — No record of observation

18 to 63 years Symptoms had been present for one to 10 years Seven cases (1, 4, 6, 7, 9, 10, and 11) showed the classical presentation with ascites, often gross, and of these six had oedema of the legs Some degree of breathlessness was usual in these patients, but it was chiefly for swelling of the abdomen or legs that they sought relief Four patients had breathlessness as their chief symptom, slight or moderate ascites was present in three of these and oedema in one All four had calcification of the pericardium and it was probably this finding on X-ray examination of the chest which led to the diagnosis Two signs were common to all our cases, namely, enlargement of the liver and engorgement of the cervical veins In all cases without ascites, or after paracentesis abdominis, a firm smooth liver edge was palpable, often as low as the level of the umbilicus, in one case pulsation of the liver was felt Engorgement of the cervical veins was not only a most valuable diagnostic sign, but the level of superficial or deep venous pulsation also provided a rough guide to the venous pressure (Lewis, 1930) In most cases the venous pressure was so high that direct readings by citrate manometer connected to a cannula in the antecubital vein exceeded the estimate made from inspection of the neck In one case there was gross enlargement of the superior and inferior epigastric veins to a degree suggestive of inferior vena caval obstruction, and likewise accompanied by an upward blood-flow, these veins became smaller after pericardectomy Pleural effusion was present in five patients In contrast to these symptoms and signs, which closely resemble those of cardiac failure, examination of the heart was largely negative No impulse could be seen or felt in most instances, nor was the heart enlarged to percussion One patient presented systolic retraction of the third and fourth interspaces, and she also had a little increase in the area of cardiac dullness Three patients had auricular fibrillation Murmurs were absent in all, but in several one or both sounds were reduplicated In five instances the pulse-volume was small and the pulse-pressure reduced X-ray examination of the chest revealed pericardial calcification in eight patients, and fluoroscopy showed diminished pulsation of the ventricles in seven out of nine patients so examined

Diagnosis A single sign, venous congestion in the neck, is invariable in constrictive pericarditis, as Volhard and Schmieden (1923) pointed out The sign is sometimes difficult to elicit when the external jugular veins are small In such instances deep venous pulsation is the chief sign, and this must be distinguished from arterial pulsation by its situation in the posterior triangle of the neck, its slow upstroke and wide amplitude, and its change of position with change of posture (Lewis, 1930) In cases of doubt it is well to measure the venous pressure directly by citrate manometer Raised venous pressure excludes cirrhosis of the liver, tuberculous peritonitis, and obstruction of the thoracic duct, three diagnoses which had previously been made in our patients, the last in a case of pseudochylous ascites More difficult to exclude may be other causes in and around the heart Subacute tuberculous pericarditis may provide an indistinguishable picture, as Cases 12 and 15 illustrate Rheumatic or congenital heart disease is easily excluded, for both have striking physical

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Mode of onset	Gradual	Sudden	Gradual	Gradual	Sudden	Gradual	Gradual	Gradual	Sudden	Gradual	Gradual
Alive or dead	A	† A	A	D	D	A	D	D	A	A	A
Venous pressure (cm. water)	10	10*	18*	8	5	15	13	10	18*	12	15
Liver enlargement	+	+	+	+	+	+	+	+	+	+	+
Ascites	+	+	+	+	0	+	+	+	+	+	+
Pleural effusion	0	R	0	0	0	0	R	R and L	R	R	0
Oedema	+	0	0	0	0	0	+	+	+	+	+
Arterial pressure	130/90	—	120/74	120/65	125/80	108/60	140/100	+	+	+	+
Cardiac irregularity	0	A F	Ex	Ex	A F	0	0	110/85	115/90	90/70	140/85
Cardio thoracic index†	44	—	50	50	48	52	52	A F	0	0	0
Diminished cardio-pulsation (X ray)	+	+	+	+	0	0	+	55	48	50	47
Pericardial calcification (X ray)	+	+	+	+	+	0	+	+	—	+	—
† Transverse diameter of heart			A F	+	+	0	+	+	0	+	0
Transverse diameter of chest × 100			+	Sign present	Ex	Ex	Extrasytokes	+	—	+	—
							0	+	By direct measurement		
							Sign absent		No record of observation		

Ascites and Venous Pressure

12	13	14	15	21	23	24	27	28		
+	+	0	+	+	+		+	+		
+	+	0	+	+	+	0	+	+		
0	0	0	Many	30	Many	0	10	5		
+	+	0	+	+	+	+	+	+		
19*	10	16 3 *	16*	7 5	7	16 5*	6	25*		
Cured	No change	Im proved	Died	Im proved	Im proved	Died	Im proved	Im proved	No change	Died
3 years	4½ years	2 months	—	2 months	8 months	—	10 months	9 months	9 months	2 weeks
0	+	0	—	0	0	—		±	+	+
0	+	0	—	0	±	—	0	0	+	+
0	6	0	—	0	0	—	0	2	4+	0
0	+	0	—	0	+	—	0	0	+	+
6*	9*	4	—	11*	16 5*	—	5	8*	No change	+

— No record of observation

† Died 3 years later

layers were $\frac{1}{4}$ to $\frac{3}{8}$ in thick, and composed of fibrous tissue with small or large areas of calcification, but without trace of any acute infective process. No abnormal adherence to the anterior chest wall was found in any case. Of the nine cases operated on, two died. One (Case 8) with gross oedema and large pleural effusions on both sides, collapsed during induction of anaesthesia. The other (Case 7), with bronchitis and emphysema, was very breathless before operation, she died of post-operative bronchopneumonia. All seven survivors of operation improved greatly. Ascites present before operation totally disappeared in six, and was much less persistent in another, oedema behaved likewise. This improvement usually began immediately after operation, but in Case 6 ascitic fluid, removed by paracentesis before operation, collected again in the next two weeks and then slowly receded. Venous pressure was reduced by operation in all cases, but it is to be noted that in all patients, whether measured indirectly from the neck or directly by manometer, it remained above the normal level even after four years (Table II). Of the technique of operation little need be said here, since the information is available elsewhere (Volhard and Schmieden, 1923, Churchill, 1936, Heuer and Stewart, 1939, Sellors, 1946, Edwards and Barlow, 1946). Particularly in gravely ill patients it is important to decide how much the patient will tolerate, and to limit operation accordingly. To avoid acute pulmonary oedema the left ventricle should be freed first, and if necessary further excision from this region and the right ventricle should be postponed to a subsequent occasion.

Mode of production of symptoms Chevers (1842) and Volhard and Schmieden (1923) attributed the chief features of constrictive pericarditis to interference with the filling of the heart during diastole, and the more detailed studies of Burwell and Blalock (1938) have largely substantiated this view. They found the venous pressure persistently raised, and equal in the arm and leg except when ascites was gross. The blood-volume was increased in two cases. The

		<i>Effects of Pericardectomy</i>							
		1	3	4	6	7	8	9	10
Before operation	Case number								
	Dyspnoea	+	+	0	+	+	+	+	+
	Ascites	+	+	+	+	+	+	+	+
	Number of paracenteses abdominis	3	0	0	2	0	0	1	1
	Oedema	+	0	+	0	+	+	+	+
Result of pericardectomy	Venous pressure (cm. water)	10	18*	8	15	13	10	18*	18*
	Time since operation	Im proved 4 months	Cured 2 years	Im proved† 2 years	Im proved 1 year 10 months	Died	Died	Im proved 6 months	Im proved 1 year 10 months
After operation	Dyspnoea	—	0	+	—	—	—	0	0
	Ascites	0	0	±	0	—	—	0	0
	Number of paracenteses abdominis	0	0	0	0	—	—	0	0
	Oedema	0	0	0	0	—	—	±	±
	Venous pressure (cm. water)	3	8*	3	0	—	—	8*	8*

* By direct measurement

+ Sign present

0 Sign absent

signs, particularly on auscultation, valvular defects are generally absent in constrictive pericarditis. Myocardial disease may be very difficult to distinguish. Slight enlargement of the heart shadow is common, the cardiothoracic ratios being 50 per cent or over in six out of 10 patients. As an example of the difficulty of distinguishing heart disease may be cited Case 6, a patient who presented slight cardiac enlargement and no pericardial calcification, and showed no definite reduction in the pulsation of the left border of the heart. She had been treated for some years as a case of heart disease at a well-known hospital for diseases of the heart. That she had probably not got cardiac failure was evident when she walked into the out-patient department for, despite enlargement of the abdomen to the size of a full-term pregnancy, there was no oedema of the legs or undue breathlessness. The typical case of constrictive pericarditis in fact differs from that of cardiac failure in the tendency for ascites to precede oedema, and in the degree of ascites and oedema that can be tolerated before the patient is immobilized by shortness of breath. One of our patients (Case 11), a travelling salesman, had been working for the previous five years, but with great difficulty owing to the enormous size of his legs and abdomen, which nearly prevented him from getting in and out of his small car. In some cases it may prove impossible to differentiate between constrictive pericarditis and myocardial disease, in these circumstances pericardial exploration may be justifiable, as Blalock and Burwell (1941) have pointed out. The diagnosis from polyserositis is discussed on page 318.

Pericardectomy and its effects Pericardial resection was performed in nine of our patients (Table II). In Case 2 it was recommended and refused. In Case 5 it was not recommended because the symptoms seemed to be due chiefly to bronchitis and emphysema, confirmed by post-mortem examination. In all 10 cases where it was examined, the pericardial sac was completely obliterated, but in one case loculi containing cholesterol crystals were found, the fused

Arterial and Venous Pressure

12	13	14	15	21	23	24	27	28		
+	+	0	+	+	+		+	+		
+	+	0	+	+	+	0	+	+		
0	0	0	Many	30	Many	0	10	5		
+	+	0	+	+	+	+	+	+		
19*	10	16 3 *	16*	7 5	7	16 5*	6	25*		
Cured	No change	Im proved	Died	Im proved	Im proved	Died	Im proved	Im proved	No change	Died
3 years	4½ years	2 months	—	2 months	8 months	—	10 months	9 months	9 months	2 weeks
0	+	0	—	0	0	—		±	+	+
0	+	0	—	0	±	—	0	0	+	+
0	6	0	—	0	0	—	0	2	4+	0
0	+	0	—	0	+	—	0	0	+	+
6*	9*	4	—	11*	16 5*	—	5	8*	No change	+

— No record of observation

† Died 3 years later

layers were $\frac{1}{4}$ to $\frac{3}{8}$ in thick, and composed of fibrous tissue with small or large areas of calcification, but without trace of any acute infective process. No abnormal adherence to the anterior chest wall was found in any case. Of the nine cases operated on, two died. One (Case 8) with gross oedema and large pleural effusions on both sides, collapsed during induction of anaesthesia. The other (Case 7), with bronchitis and emphysema, was very breathless before operation, she died of post-operative bronchopneumonia. All seven survivors of operation improved greatly. Ascites present before operation totally disappeared in six, and was much less persistent in another, oedema behaved likewise. This improvement usually began immediately after operation, but in Case 6 ascitic fluid, removed by paracentesis before operation, collected again in the next two weeks and then slowly receded. Venous pressure was reduced by operation in all cases, but it is to be noted that in all patients, whether measured indirectly from the neck or directly by manometer, it remained above the normal level even after four years (Table II). Of the technique of operation little need be said here, since the information is available elsewhere (Volhard and Schmieden, 1923, Churchill, 1936, Heuer and Stewart, 1939, Sellors, 1946, Edwards and Barlow, 1946). Particularly in gravely ill patients it is important to decide how much the patient will tolerate, and to limit operation accordingly. To avoid acute pulmonary oedema the left ventricle should be freed first, and if necessary further excision from this region and the right ventricle should be postponed to a subsequent occasion.

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cardiac output was always low. Exercise did not increase stroke output, and since these patients had tachycardia at rest, there was very little rise in total cardiac output. Raised venous pressure associated with increased blood-volume may be regarded as a compensatory device to raise cardiac output. Raised pressure in the veins entering the right auricle would explain enlargement of the liver, ascites, and oedema, and in the pulmonary veins, dyspnoea. From this it might be assumed that patients showing dyspnoea as a chief symptom would have a predominant encasement of the left ventricle. We have obtained no evidence of this, rather has it seemed to us that unusual degrees of breathlessness in constrictive pericarditis have been associated with bronchitis and emphysema. In heart failure increased venous pressure and diminished cardiac output presumably arise from diminished contractility of the heart muscle, in constrictive pericarditis they arise from the constriction exerted by the dense pericardium, as is evident by the return of these values towards normal after pericardectomy (Burwell and Blalock, 1938). Nevertheless, the circulatory disturbances are qualitatively similar in the two conditions, and it is not clear why ascites should be so much more conspicuous in constrictive pericarditis than in cardiac failure. We have noticed that venous pressure is as a rule higher in patients with constrictive pericarditis than in those with cardiac failure. We reject as a cause intrathoracic constriction of the inferior vena cava by the pericardial disease, firstly, because in Case 6 pulsation of the liver was clearly felt, and secondly, because pericardectomy, which frees only the ventricle, commonly reduces venous pressure and abolishes ascites. A more critical and detailed study than has yet been made may answer this interesting question.

Onset of symptoms. It is generally accepted that constrictive pericarditis is the sequel to an earlier acute lesion. In all our cases symptoms seem to have developed a considerable time after the acute pericarditis, they certainly did in Case 10, in which symptoms appeared two years before X-ray examination of the chest showed pericardial calcification. It would therefore be expected that symptoms would develop gradually as the scar tissue around the heart gradually compressed it. This was so in eight cases, but in the three following instances the onset was abrupt.

Case 2. A labourer, aged 62 years, suddenly became breathless at work, he was able to resume work after a fortnight's rest. Four months later he again became breathless and noticed swelling of the legs. This patient had auricular fibrillation, and it is possible that the sudden onset of this condition precipitated his symptoms.

Case 5. A labourer, aged 46 years, had a bout of coughing when on night duty, when he mounted his bicycle to go home he suddenly became breathless and had to dismount, recovering his breath in about a quarter of an hour. Subsequently he was always breathless on exertion. This man, when seen four months later, presented extensive pericardial calcification, but in addition, chronic bronchitis and emphysema, auricular fibrillation, and a reticulosis from which he subsequently died. In this case the acute symptoms may

have been precipitated by the development of acute bronchitis or auricular fibrillation

Case 9 A newsagent, aged 52 years, went out to deliver his evening papers as usual. When he had walked about 20 yards he suddenly felt unable to get his breath, and had a heavy feeling, more discomfort than pain, in his abdomen. He had to stop and rest against a fence for some minutes. With great effort he managed to complete his round of one and a half miles, but the breathlessness and hypogastric discomfort continued until he went to bed. On the following morning he noticed nothing abnormal, but two days later his feet began to swell during the day, going down at night, and then his abdomen swelled. From this time oedema and ascites increased steadily until pericardectomy eight months later, after which they disappeared in the next three months. While in hospital this patient presented no signs other than those of chronic constrictive pericarditis with calcification. Yet some acute morbid event affecting the action of the heart must have precipitated the development of the symptoms. This may have been a coronary artery thrombosis, for, as Blumgart, Schlesinger, and Zoll (1941) have shown, this condition is much more common than was previously thought and is frequently not accompanied by myocardial infarction with its attendant symptom complex.

It has already been noted that pericardectomy usually abolished ascites and oedema, but that the venous pressure, though reduced, remained above normal. Thus it is possible for the patient with constrictive pericarditis to have no symptoms even though the venous pressure is raised. It seems probable that the patient developing constrictive pericarditis may pass through a similar phase, perhaps lasting many years, during which the venous pressure is raised, but other symptoms have not yet developed. Further progress of cardiac compression or any sudden event interfering with the action of the heart may precipitate oedema, ascites, and breathlessness.

The relationship of constrictive pericarditis to other forms of adherent pericardium. We agree with Volhard and Schmieden (1923) that there are three chief forms of chronic pericardial disease that are distinct clinically and probably also in pathogenesis. The first or asymptomatic form has no clinical consequences and is recognizable only *post mortem*, when the pericardial cavity is found to be wholly or partly obliterated by fine adhesions. The parietal and visceral layers are not thickened and not adherent to the surrounding structures. This form can result from myocardial infarction and probably from other causes. The second or internal form is constrictive pericarditis or *concretio cordis*. Here the heart is of normal or reduced size and is encased in a greatly thickened dense fibrous pericardium not adherent to the chest wall, though it may be attached to the adjacent lung and pleura. The clinical features of this form have been described. We submit later in the present paper that it is usually, if not always, the result of past tuberculous infection. The third or external form has been called *accretio cordis*. Here the heart is usually enlarged, often grossly, and is encased in a moderately thickened pericardium, the two layers of which are everywhere adherent. The pericardium is attached in some

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Case 2. A labourer, aged 62 years, suddenly became breathless at work, he was able to resume work after a fortnight's rest. Four months later he again became breathless and noticed swelling of the legs. This patient had auricular fibrillation, and it is possible that the sudden onset of this condition precipitated his symptoms.

Case 5. A labourer, aged 46 years, had a bout of coughing when on night duty, when he mounted his bicycle to go home he suddenly became breathless and had to dismount, recovering his breath in about a quarter of an hour. Subsequently he was always breathless on exertion. This man, when seen four months later, presented extensive pericardial calcification, but in addition, chronic bronchitis and emphysema, auricular fibrillation, and a reticulosis from which he subsequently died. In this case the acute symptoms may

Riesman (1901) was one of the first to point out that there were two forms of adherent pericardium clinically distinguishable, the rheumatic form with a large heart, valvular murmurs, and a rheumatic history, and the tuberculous form, with a small heart, no murmurs, and early ascites, but it is chiefly to the clinical acumen of Volhard and Schmieden (1923) that we owe the clear recognition that there are distinct types of adherent pericardium, and the sign, venous congestion in the neck, by which concretio cordis can be distinguished from cirrhosis of the liver. Before Volhard and Schmieden's paper, constrictive pericarditis was almost entirely a post-mortem diagnosis. Pick (1896), it is true, had diagnosed his third case during life because a pericardial rub had been heard before ascites developed, but he wrote, 'The following points are important in the differential diagnosis (a) absence of an aetiological factor for cirrhosis of the liver, (b) history of a previous pericarditis, (c) earlier occurrence of oedema of the legs'. It is easy to see how little help these points were to the physician in making a diagnosis. It is not surprising that Delorme (1898) and Beck (1901) were unable to carry out the operations which they had devised to relieve constrictive pericarditis because they received no patients from the physicians. In more recent years analysis of post-mortem material by Hosler and Williams (1936) and Armstrong (1940) has emphasized the distinction between the rheumatic and other forms of chronic pericardial disease. Hosler and Williams found 75 cases of cardio-pericardial adhesions in 4,400 post-mortem records at Cleveland, of these 54 had cardiac hypertrophy and valvular and rheumatic heart disease, 21 had no cardiac enlargement and no valvular or myocardial disease. Armstrong, analysing 114 autopsy cases of adherent pericardium at the London Hospital, found that 72 had large hearts, but these were always associated with rheumatic carditis. Thirty-one had no symptoms and six had constrictive pericarditis. He considered that the constrictive group and the rheumatic group were quite distinct histologically, the former showing thick scar tissue with dense collagen, while in the latter the adhesions were thinner and contained delicate collagen. There is, then, no doubt that constrictive pericarditis is quite distinct from rheumatic pericarditis. It is important that this distinction should be recognized. The term 'adherent pericardium', combining two totally distinct maladies, should be abandoned.

Aetiology Constrictive pericarditis is not due to rheumatic infection. Clinically, the rheumatic form of adherent pericardium is quite different. The final proof has been given by White (1935) and Harrison and White (1942), for a follow-up of 1,500 cases of rheumatic heart disease revealed no case of constrictive pericarditis. The acute pericarditis occurring with uraemia may also be excluded, for it is usually terminal and there is no evidence of present or past renal disease in constrictive pericarditis. Pericarditis due to myocardial infarction may also be excluded, because of the age incidence, and because myocardial infarction has not been found in constrictive pericarditis. Finally, pericarditis due to malignant metastasis may be excluded. Constrictive pericarditis must be the result of one of the remaining forms of acute pericarditis, namely, tuberculous, septic, or due to some unascertained cause. We have

not pathognomonic, physical signs, namely, systolic retraction of the ribs and rib spaces, particularly the third and fourth, immobility of the impulse with change of posture, and pulsation of the left lower ribs posteriorly (Broadbent, 1895) There are also signs of valvular disease and cardiac failure This form is always or nearly always rheumatic

Much of the confusion surrounding chronic pericardial disease is terminological and results from the use of the terms 'mediastino-pericarditis' and 'adherent pericardium' to describe sometimes one and sometimes the other of these two distinct maladies, accretio and concretio cordis Thus, mediastino-pericarditis is used by both White (1944) and Lewis (1946) with reference to concretio cordis and by Volhard and Schmieden (1923) and Blalock and Burwell (1941) with reference particularly to accretio cordis

The terms 'adhesion of the pericardium' and 'adherent pericardium' have long caused confusion Over a century ago Hope (1832) stated that he had 'never examined after death a case of complete adhesion of the pericardium without finding enlargement of the heart' Chevers (1842) considered that these remarks could be applied only to one class of case, 'to those in which, superadded to the adhesion of the pericardium, there is also disease of the valvular passages of the heart, these cases are certainly the most frequent' He then described four cases of adherent pericardium in which the heart was not enlarged These were all diagnosed *post mortem* and were all what we should now recognize as constrictive pericarditis He stated that the Museum Inspection Book at Guy's Hospital contained no record in the previous seven years of enlargement of the heart associated with long-standing obliteration of the pericardial cavity in which the valves were healthy, and supported this statement by analysing 47 cases Chevers's analysis clearly demonstrated that those cases having enlargement of the heart and valvular disease, which we would now recognize as rheumatic, were anatomically distinct from those cases having small hearts and no valvular disease, which we would now recognize as the asymptomatic and constrictive forms The conclusion that there were at least two distinct clinical entities was not drawn by Chevers (1842) or Wilks (1870), though Wilks first clearly recognized the distinctive clinical features of constrictive pericarditis, 'one of the causes which lead to impairment of the heart's action with the accompaniments of venous congestion and dropsy' Wilks, however, did point out that simple pericardial adhesions produced no ill effects and were often found unexpectedly *post mortem* The confusion was further perpetuated by Broadbent's (1895) book where the rheumatic and constrictive forms were described together without any attempt at distinction, for of Broadbent's 12 recorded cases, 10, all with large hearts, were of the rheumatic type, and two with small hearts were of the constrictive type Because the different types had not been clearly distinguished, text-book descriptions of adherent pericardium were of the type which the physician could diagnose during life, namely, the rheumatic form with its numerous signs Even to-day it is exceptional to find a clear distinction drawn between accretio and concretio cordis in text-books of general medicine or cardiology

Case 13 A girl, then aged 11 years, was admitted to Cheltenham Hospital on August 18, 1941. Her brother had been in a sanatorium, from which he had recently been discharged. Eight weeks previously she had developed a dry cough and shortness of breath, and had become tired and depressed. She was sent to the Tuberculosis Officer, who X-rayed her chest on July 25, this showed a pericardial effusion, small bilateral pleural effusions, and an area of consolidation in the right middle zone. She had been in bed at home since her illness began. On admission she was an ill child, thin and blue, with signs of a large pericardial effusion and oedema of the ankles. There was no fever, but the pulse ranged between 110 and 130. During her stay in hospital the oedema of the legs subsided and the pleural effusions disappeared, but the pericardial effusion remained. She was transferred to Harefield Hospital on 15.10.41. When first seen, she was a weakly child playing with other children in the hospital corridor, and was afebrile. To our surprise she presented gross venous congestion in the neck, cardiac dullness extending from the right mid-clavicular line to the left posterior axillary line, and a liver reaching to the umbilicus. Dilated veins were visible over the front of the chest. There were no cardiac murmurs, and oedema and ascites were absent. The arterial pressure was 86/66. Screening showed an enormous heart shadow (Plate 22, Fig. 1) with no pulsation. Pericardial aspiration yielded one and a half pints of straw-coloured fluid containing 7 gm of protein per 100 c.c. and an excess of lymphocytes, no tubercle or other bacilli were isolated on culture. After air replacement of the fluid a thickened parietal pericardium (Plate 22, Fig. 2) was revealed, and a healing tuberculous lesion in the right upper zone (Plate 23, Fig. 4) was seen on X-ray. Subsequent examinations showed progressive calcification of this focus (Plate 23, Fig. 5). The heart shadow progressively decreased in size, but signs of cardiac compression persisted. On April 23, 1942, the pericardium was explored. It was 1 cm thick, and the outer layer removed from over the anterior surface of the ventricles separated easily from the inner, leaving a shaggy white surface covered with caseous tuberculous material, there was no fluid. Section showed granulation tissue with giant cells and scattered tubercles (Plate 24, Fig. 6). A post-operative left pleural effusion was absorbed (Plate 22, Fig. 3) and she left hospital in January, 1944, still with venous congestion, enlarged liver, and moderate ascites. After she attempted light work in June, 1945, the size of her abdomen and legs increased and she developed a painful swelling of the left thigh. She was readmitted in September, 1945, with gross ascites and slight oedema of the legs. Venous congestion in the neck was 12 cm and the liver edge was felt 10 cm below the costal margin in the mid-clavicular line. The cardiac impulse was 11 cm from the mid-line in the fifth space, and the pulmonary second sound accentuated and reduplicated. The pulse was 90 to 100, temperature normal, and arterial pressure 110/70, there was no pulsus paradoxus. A large brawny swelling on the lateral aspect of the left thigh yielded on aspiration creamy pus from which tubercle bacilli were recovered by guinea-pig inoculation. X-ray examination showed periosteal elevation at the upper end of the left femur. She was kept in bed on restricted fluids and repeated injections of mersalyl. The cold abscess gradually resolved, but ascites increased, followed by signs of a right and, later, a left pleural effusion. On November 28, 1946, the pericardium was exposed by postero-lateral thoracotomy. Dense adhesions were encountered between pericardium, lung, and chest wall. Despite this, the pericardium was dissected off the anterior, posterior, and left lateral surfaces of the ventricles, and from the region of the apex, the left phrenic nerve being cut. Tuberculous tissue was again encountered (Plate 24, Fig. 7). Post-operative progress was satisfactory, a left pleural effusion being

found, as others have, that neither the histology of the pericardial scar tissue nor the patient's history provides clear evidence of causation. No patient gave a history of past acute pericarditis. Only one (Case 11) had had a severe pyococcal illness. Three had had pleurisy, two haemoptysis, and one acute bronchitis many years before the onset of constrictive symptoms. The remainder had had no illness that could be construed as relevant. To find the cause of constrictive pericarditis it is necessary to begin at the beginning and find out what happens to the relevant kinds of acute pericarditis in later years. We therefore now present all the cases of acute tuberculous, septic, and idiopathic pericarditis seen by us over a seven-year period, together with their later history.

Acute Tuberculous Pericarditis

Without tuberculous infection of other serous cavities. The four cases in this group provide features of such importance to the conception of constrictive pericarditis that they may be briefly described here.

Case 12. A youth, aged 17 years, after giving a false age, was passed fit for service with the Royal Marines in May, 1943. A month after enlistment, while on a physical training course, he noticed swelling of his ankles, for which he was given local treatment. A few days later, on a training run, he had to drop out because of breathlessness and severe pain in the abdomen. He was admitted to the sick bay and transferred to Haslar Hospital with a diagnosis of deep varicose veins. He was transferred to Park Prewett Hospital in July, 1943, there diagnosed by Dr. Laurent as a case of constrictive pericarditis, and sent to Harefield Hospital on October 25. During his stay at Park Prewett Hospital he had been afebrile, but his oedema and breathlessness on exertion had increased. On admission to Harefield Hospital he showed slight oedema of the legs and sacrum, slight ascites, and a small right pleural effusion. Faint venous pulsation was visible in the neck 12 cm. above the angle of Louis, the venous pressure by direct measurement being 19 cm. The liver was palpable 5 cm. below the costal margin in the mid-clavicular line. The pulse was small and paradoxical and the arterial pressure 120/80. The cardiac impulse was just palpable in the fifth space within the mid-clavicular line, the cardiac dullness was increased to the right but not upwards, and the heart sounds were normal. A chest X-ray showed a broad upper mediastinal shadow, a transverse diameter of heart 12.5 cm. and of chest 27.5 cm. There was evidence of congestion of the lungs. A kymogram showed a little pulsation of the heart shadow. As the patient was afebrile and seemed to be suffering from chronic constrictive pericarditis, pericardectomy was performed on 16.12.43, the pericardium being removed over the right and left ventricles anteriorly, and the left ventricle laterally as far as the phrenic nerve. The pericardium was white, thickened, and immobile. The plane of cleavage was through active caseous tuberculous tissue containing some fluid. The pericardium was 3 to 4 mm. thick, and sections showed many tuberculous giant cell systems with abundant fibrosis. After operation there was slight pyrexia for 10 days, and the left pleura was aspirated four times. His subsequent progress was entirely satisfactory. When last seen in October, 1946, he had had no recurrence of tuberculosis, and felt well. A chest film showed no significant abnormalities, and on screening there was free pulsation of the right and left borders of the heart and the left ventricle posteriorly. The liver was not palpable, and the venous pressure 8 cm. above the angle of Louis by direct measurement.

Tissue removed from the region of the cardiac apex showed calcification. Microscopy of the pericardium showed acute caseating tuberculosis. After operation he rapidly improved. On discharge on June 10, 1947, he was up all day and had no oedema or ascites, but still had small pleural effusions on both sides. The venous pressure had fallen to 11 cm, and vital capacity risen from 800 to 1,000 c.c. In January, 1948, it was reported from the Royal Infirmary, Aberdeen, that the liver remained enlarged about 8 cm below the costal margin. The heart was normal in size. X-ray showed bilateral chronic pleurisy. His only symptom was oedema of the ankles at the end of the day.

These four cases have impressed us with the difficulty of diagnosing acute tuberculous pericarditis. The difficulty arises specially from the relatively slight subjective disturbances that may accompany the malady. Thus, in Case 12, acute pericarditis seems to have been present for several days during which the patient was participating actively in physical training for the Royal Marines, no mean test of physical fitness. Case 13, at the time when she first came under our care, presented such a contrast between her apparent well-being and the enormous size of the cardiac dullness that one of us (G. W. P.) who had not previously encountered acute tuberculous pericarditis did not seriously entertain the diagnosis of pericardial effusion until the chest was screened. When venous congestion and its attendant symptoms are gross, acute tuberculous pericarditis may thus be diagnosed as chronic constrictive pericarditis, as occurred in Cases 12 and 15. Case 15 was particularly surprising, for it seemed probable from the history that this was an undoubted case of constrictive pericarditis resulting from a staphylococcal infection. When symptoms of venous congestion are slight or absent, the pericarditis will probably be overlooked. Finally, with high fever and a large effusion, a left pleural effusion may be diagnosed, as in Case 14. This diagnosis may not be corrected until an X-ray examination of the chest is made.

Tuberculous pericarditis with involvement of serous cavities. Tuberculous polyserositis (Cases 16 to 31). Collections of fluid in the pleural and peritoneal cavities may occur in tuberculous pericarditis as a result of mechanical factors only, for these collections follow rather than precede pericardial disease, subside when the thick pericardium is resected, and provide no evidence in life or after death of tuberculous infection. Such were the effusions in the four cases just described. More frequently these effusions are due to active tuberculosis of the serous membranes, as is shown by their preceding the pericarditis, or by the recovery of tubercle bacilli from them, or by post-mortem. We have summarized 16 cases of this kind in Table III. These include two cases in which there was no clinical pericardial tuberculosis, although in one a few tubercles were found in the pericardium at autopsy. Tuberculosis was proved in 12 cases and probable in four (Cases 28, 29, 30, and 31). These cases resemble those of tuberculous pericarditis without involvement of other serous cavities in their age and sex distribution, in the course of the pericarditis, and in its response to surgery. They differ in presenting a picture of a much more serious disease with prolonged fever, wide dissemination of tuberculous infection, and a poor prognosis. The chief features of tuberculous polyserositis are as follows.

absorbed and ascites and oedema disappearing. By June, 1947, she was up for most of the day, with no ascites or oedema. Venous pressure was 4 cm above the angle of Louis. Kymography showed that the left border of the heart, which had been almost stationary before operation, pulsated freely. In February, 1948, she had no venous congestion, ascites, or oedema, and the liver was normal in size.

Case 14 A capstan operator, aged 17 years, noticed pain in the left side of his chest in July, 1945. He was admitted to Paddington Hospital on July 30, 1945, with signs of a left pleural effusion. He had a temperature of 103° F and looked ill. On August 1 a chest X-ray showed a very large heart shadow, almost certainly a pericardial effusion, and on August 3 aspiration of the pericardium yielded clear yellowish fluid which was sterile on culture. The fever lasted a month, gradually declining, and the erythrocyte sedimentation rate reached normal on October 25, when he was allowed up. In November, 1945, he was transferred to Harefield Hospital. On admission he had no symptoms and no pyrexia, oedema, or ascites, the erythrocyte sedimentation rate was 5 mm in one hour. The pulse was 108, and paradoxical, venous pulsation was 5 cm above the angle of Louis, and the liver edge palpable 4 cm below the costal margin. The cardiac impulse was 11 cm from the mid-line in the fourth space, and pulsation of the second and third left costal cartilages near the sternum was visible and palpable. The second sound was reduplicated at the base. X-ray examination showed some enlargement of the cardiac shadow with restricted pulsation of its borders. Venous pressure by direct measurement was 16 cm. The patient stopped breathing during induction of anaesthesia for pericardectomy on 11.2.46, and despite cardiac massage died. Post-mortem examination showed a right apical tuberculoma, one tuberculous tracheo-bronchial lymphnode, nutmeg liver, and fibrocaseous tuberculosis of the pericardium, the two layers being everywhere adherent.

Case 15 A boy of 11 years was healthy until in September, 1945, he developed boils on his neck, accompanied by fever. *Staphylococcus aureus* was grown from the pus. One week later he was admitted to the Royal Aberdeen Hospital for Sick Children, where he was noted to be ill and breathless and had high fever. He had the clinical and X-ray signs of pericardial and pleural effusions, and a lymphnode on the left side of his neck discharging pus, from which *Staphylococcus aureus* was grown. Clear yellow pleural and blood-stained pericardial fluids were sterile on culture. A blood-culture was also sterile. He was treated with penicillin and sulphathiazole for a week, without any effect on the pyrexia, which subsequently declined to about 100° F by the beginning of October and to normal by the beginning of December. He was discharged home on December 20. In March, 1946, he became breathless on exercise, and his ankles and abdomen swelled. In April, 1946, he was readmitted to the Hospital for Sick Children and found to have bilateral pleural effusions, ascites, and a liver edge a hand's breadth below the costal margin. After treatment with mersalyl he was advised to have surgical treatment, and was sent to Harefield Hospital in November, 1946. He showed the typical picture of constrictive pericarditis. He was afebrile. He had gross ascites and oedema, bilateral pleural effusions, and enlargement of the liver to the umbilicus. The heart was not enlarged and there were no murmurs. His venous pressure by direct measurement was 16 cm of water. On February 17, 1947, operation by the left anterior approach exposed a densely fibrotic left pleura. Densely fibrotic pericardium about 0.5 cm thick was excised from the anterior surface of the ventricles and the left border and posterior surface of the left ventricle.

Tuberculous Polyserositis

IV[illegible]

TABLE

Clinical Features of

Case number	16	17	18	19	20	21	22
Sex and age (at onset)	M 40	F 10	M 17	M 20	M 19	M 17	M 20
Onset to death or last observation	10 months	2 years	2 years 3 months	8 months	2 years	5 years 8 months	3 years 5 months
Early symptoms	Pleural pain, fever	Pleural pain cough, fever	Chills, abdominal pain	Stiff legs, loss of weight	Pleural pain, hæmoptysis	Ascites, dyspnoea	Fatigue, abdominal pain
Alive or dead	D	D	D	D	D	A	D
Tuberculous sclerosis proved	+	+	+	+	+	+	+
Pericardial effusion	+	+	+	+	+	+	+
Pleural effusion	R	R & L	R & L	R & L	R & L	R & L	R & L
Ascites	+	+	+	+	+	+	doughy
Oedema	+	+	+	+	+	+	-
Pulmonary tuberculosis	0	+	+	+	+	+	+
Other tuberculous lesions	Mediastinal lymph nodes, liver, spleen	Spine, kidneys, probably meninges	Gut, lymph nodes, brain, miliary	Liver, spleen	Brain, lymph nodes, kidney, spleen, miliary	0	Urogenital, lymph nodes
Temperature *F (during pyrexia)	100 to 102	102	100	100	100 to 102	99.5	100
Erythrocyte sedimentation rate (Westergren)	94 to 137	47	17	-	44	7 to 32	51
Pericardial effusion absorbed	+	+	+	+	+	+	+
Constrictive pericarditis	+	+	+	+	+	+	+
Cardio thoracic index*	55	55	47	-	42	47	46
Arterial pressure (mm Hg)	-	120/90	95/70	105/70	100/85	96/75	125/75
Venous pressure (cm water)	+	0	10	+	11†	7.5	25†
Cardiac irregularity	A.F.	0	0	0	0	0	0
Pericardial calcification	0	0	0	0	0	0	0

* Transverse diameter of heart
Transverse diameter of chest $\times 100$

- No record of observation.

† By direct measurement

TABLE

Characters of Serous Fluids in

Case number	16	17	18	19	20	21
Number of serous cavities affected	4	4	4	4	4	4
Order of involvement	Pericardium	3	2	3	2	3
	Pleurae	1	2	1	1	2
	Peritoneum	2	3	1	3	1
Appearance	-	-	Bl. st	-	Bl. st.	-
Protein gm per 100 c.c.	-	-	3 to 5	-	4	-
Cells per c mm	-	-	Scanty	-	900	-
Type of cell	-	-	75% P	-	82% P	-
	-	-	25% L	-	12% L.	-
Tubercle bacilli cultured	-	-	+	-	+	-
Guinea pig inoculation	-	-	0	-	-	-
Pericardial tubercles	+	+	+	+	+	+
Appearance	Straw	Bl. st	Straw	Straw	Straw	Straw
Protein gm per 100 c.c.	-	-	1.5 to 3	-	1.2 to 3.6	0.4 to 2.4
Type of cell	P L	99% L	P L	R.B.C L.	R.B.C P L E	P L E
Cells per c mm	Scanty	-	Scanty	-	Scanty	Scanty
Tubercle bacilli cultured	0	-	0	+	+	0
Guinea pig inoculation	0	0	+	+	+	0
Pleural tubercles	+	-	+	+	+	+
Appearance	Straw	-	-	Straw	Straw	Straw
Protein gm per 100 c.c.	-	-	-	-	3.7 to 4.2	0.6 to 2.2
Cells per c mm	Scanty	100	-	-	2800	Scanty
Type of cell	L	98% L	-	R.B.C E P	R.B.C P L E	L. E.
Tubercle bacilli cultured	-	-	-	0	0	0
Guinea pig inoculation	+	+	+	+	0	+
Peritoneal tubercles	-	-	-	-	-	-

- No record of observation

P Polymorphonuclears
L Lymphocytes

Age and sex Ages varied from four to 49 years, and averaged 21 years By contrast, Blalock and Levy (1937) and Keefer (1937), in the south and north of the United States of America respectively, have described tuberculous pericarditis as essentially a disease of old men Thirteen of our cases were male and three female A similar preponderance of male patients with tuberculous pericarditis has been noted by Blalock and Levy (1937) (19 male, 3 female), Harvey and Whitehill (1937) (90 per cent male), Heimann and Binder (1940)

TABLE VI

Protein Contents (gm per 100 c c) of Exudates and Transudates

Fluid	Exudates			Transudates		
	Number of cases	Protein		Number of cases	Protein	
		Range	Average		Range	Average
Pleural	5	0.9 to 3.6	2.0	3	0.5 to 3.6	1.9
Peritoneal	5	0.5 to 4.0	2.0	4	0.5 to 5.25	2.1

(23 male, 8 female), Keefer (1937) (17 male, 3 female), Norris (1904) (86 male, 11 female), and Osler (1893) (13 male, 4 female)

Order of involvement of serous cavities Pleural effusions developed in all cases, bilaterally in 13 and unilaterally in three Ascites occurred in 12 and peritoneal tuberculosis was found in two more cases *post mortem* Pericardial effusion occurred in 14 The earliest effusion was pleural in seven cases, peritoneal in three, and pericardial in one At the first examination pleural and pericardial effusions were both present in four cases, and pleural and peritoneal effusions in one (Table IV)

Character of the fluid The characters of the fluids are summarized in Table IV. Blood-stained fluid was found in five of seven pericardial fluids, in two of 15 pleural fluids, and never in ascitic fluid The chief interest in these fluids lies in the information which they give as to whether or not they arose from active tuberculosis In differentiating between transudates and exudates, it is usual in this country to rely on protein content, whether determined directly, or indirectly by specific gravity It is therefore of interest to compare the pleural and peritoneal fluids in those cases of tuberculous polyserositis where either post-mortem examination or the recovery of tubercle bacilli proved their inflammatory origin (Table IV) with the corresponding fluids obtained from the cases of constrictive pericarditis and tuberculous pericarditis without other serous cavity inflammation (Table V) In the last two groups the absence of tubercle bacilli and the rapid disappearance of the fluid after pericardectomy are the main evidence for the fluid being a transudate The protein contents of exudates and transudates so recognized are summarized in Table VI It will be seen that there is no difference between them, either in the range or the average values There are two possible causes for this result In the first place it is possible that infection played only a minor part in determining the collection of fluid in our patients. No fewer than 12 of the patients with polyserositis had oedema It may be that the factors concerned in oedema

TABLE V
Characters of Serous Fluids in Tuberculous Pericarditis and Chronic Constrictive Pericarditis

Case number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Pericardial fluid	Appearance	—	—	—	—	—	—	—	—	—	—	Straw	Straw	Straw
	Protein gm per 100 c c	—	—	—	—	—	—	—	—	—	—	—	7	—
	Cells per c mm	—	—	—	—	—	—	—	—	—	—	Scanty RBC	Scanty RBC	Scanty P.
Pericardial fluid	Type of cell	—	—	—	—	—	—	—	—	—	—	Scanty RBC	Scanty RBC	Scanty P.
	Tubercle bacilli cultured	—	—	—	—	—	—	—	—	—	—	0	0	0
	Tubercle bacilli cultured	—	—	—	—	—	—	—	—	—	—	+	+	+
Pleural fluid	Appearance	—	—	—	—	—	—	—	—	—	—	—	—	—
	Protein gm per 100 c c	—	—	—	—	—	—	—	—	—	—	—	—	—
	Cells per c mm	—	—	—	—	—	—	—	—	—	—	—	—	—
Pleural fluid	Type of cell	—	—	—	—	—	—	—	—	—	—	—	—	—
	Tubercle bacilli cultured	—	—	—	—	—	—	—	—	—	—	—	—	—
	Tubercle bacilli cultured	—	—	—	—	—	—	—	—	—	—	—	—	—
Pleural fluid	Appearance	—	—	—	—	—	—	—	—	—	—	—	—	—
	Protein gm per 100 c c	—	—	—	—	—	—	—	—	—	—	—	—	—
	Cells per c mm	—	—	—	—	—	—	—	—	—	—	—	—	—
Ascitic fluid	Type of cell	—	—	—	—	—	—	—	—	—	—	—	—	—
	Tubercle bacilli cultured	—	—	—	—	—	—	—	—	—	—	—	—	—
	Tubercle bacilli cultured	—	—	—	—	—	—	—	—	—	—	—	—	—
Peritoneal fluid	Appearance	—	—	—	—	—	—	—	—	—	—	—	—	—
	Protein gm per 100 c c	—	—	—	—	—	—	—	—	—	—	—	—	—
	Cells per c mm	—	—	—	—	—	—	—	—	—	—	—	—	—
Peritoneal fluid	Type of cell	—	—	—	—	—	—	—	—	—	—	—	—	—
	Tubercle bacilli cultured	—	—	—	—	—	—	—	—	—	—	—	—	—
	Tubercle bacilli cultured	—	—	—	—	—	—	—	—	—	—	—	—	—

* Guinea pig inoculation also negative

RBC Red blood corpuscles P Polymorphonuclears E Endothelial cells L Lymphocytes
 + Sign present 0 Sign absent — No record of observation
 Straw Straw coloured fluid.

tuberculosis, tubercle bacilli were demonstrated by gastric lavage, *post mortem* a caseous lesion was found in the right upper lobe. In Case 25, towards the end of the illness, a positive sputum and active infiltration were found, while *post mortem* miliary tuberculosis was present, Case 27 showed a positive sputum. In three cases without clear radiological or other evidence of pulmonary tuberculosis during life, this was found *post mortem*. The lesions consisted of recent bronchopneumonic tuberculosis (Case 26), and recent miliary tuberculosis in Cases 18 and 19, with older apical lung tubercles in Case 18. No tuberculous lesion was found in the lungs of Cases 16 and 23, but in the latter the post-mortem examination, done outside the hospital, was not conclusive. Case 31 is still alive and presents no conclusive clinical evidence of pulmonary tuberculosis. Pulmonary tuberculosis was found in 65 of Norris's (1904) 82 cases of tuberculous pericarditis. In all our cases coming to *post mortem*, except Case 23 in which information is defective, caseous tuberculosis of the tracheo-bronchial and other mediastinal lymphnodes was found.

Other tuberculous lesions In six cases tuberculous lesions other than pulmonary were found during life. Thus Case 17 developed a psoas abscess with caries of the first and second lumbar vertebrae 15 months after the onset, eight months later tubercle bacilli were found in the urine, and one month after this she died, with the clinical features of tuberculous meningitis. No post-mortem examination was allowed. In Case 29 cervical adenitis developed 15 months after the onset, the biopsy showing caseating tuberculous tissue, one month later a cold abscess appeared over the left tibia, and tubercle bacilli were grown from the pus. Case 18 appeared to be progressing favourably until 18 months after the onset, when recurrence of pyrexia, with headache, vomiting, and neck rigidity heralded the onset of tuberculous meningitis, proved *post mortem*, together with widespread miliary tuberculosis. Case 22 developed tuberculous epididymitis four years from the onset and died with extensive urogenital tuberculosis. Case 24 developed a tuberculous knee-joint 18 months from the onset. Case 30 developed signs of tuberculous arthritis two years from the onset, both elbows and the left knee being involved, with subsequent discharge from the right elbow, two years later there was severe limitation of movement in the elbows and knee. Although the pus from the joint was not examined, the X-rays were typical of tuberculous disease. The patient died in April, 1947, but no details were available. In addition to these six, a wide haematogenous spread of tuberculosis was found in a further four cases *post mortem*.

General clinical features The onset is usually insidious, with malaise, chills, sweats, pleural pain, cough, or dyspnoea. First examination may reveal only a pleural or pericardial friction rub, but in the course of a few days this is replaced by signs of effusion, in the case of the pericardium by venous congestion in the neck, enlargement of the liver, and the characteristic area of cardiac dullness. Fever varying in the day from 100° to 102° F or more is common, but later hectic variations are of grave import. Within the course of a few months further serous cavities become involved, until finally the patient has signs of pleural and pericardial effusions and ascites, and usually

formation, such as raised venous pressure and perhaps reduction in the plasma-protein, were of more importance in causing pleural and peritoneal collections of fluid than active inflammation. In the second place it is probable that in a given case the protein content of a fluid may be influenced by other factors that are not yet perfectly understood. According to Keefer (1937), the protein content of a transudate may rise after prolonged treatment with mercurial diuretics. This may be the explanation in the following case, which demonstrates the fallacy of differentiating transudates and exudates on protein content alone.

A woman of 50 years with degenerative heart disease and auricular fibrillation developed gross oedema and ascites, for which she was treated for some weeks at home with mercurial diuretics. As she made little progress, she was admitted to hospital, and the first paracentesis abdominis yielded 13 pints of fluid with a protein content of 6.5 gm per 100 c.c. In specimens of fluid obtained subsequently the protein varied from 2.5 to 4 gm per 100 c.c.

Attempts to recover tubercle bacilli by culture or guinea-pig inoculation from cavities shown at operation or autopsy to be infected with tuberculosis frequently fail. Fluid obtained from seven pericardial cavities with proved tuberculosis gave negative results in five and positive results in two on culture, and two negative and one positive on guinea-pig inoculation. The results on fluids obtained from eight pleural and nine peritoneal cavities were similarly unsatisfactory. The difficulties of demonstrating tubercle bacilli in a fluid are well shown in Case 18, in which tuberculosis of all four serous cavities was found *post mortem*. In this case pleural fluid gave a negative culture eight times, a negative result to guinea-pig inoculation twice, and a positive result once, pericardial fluid gave two negative cultures, and one positive and one negative result to guinea-pig inoculation. Evidently bacilli are not numerous in such fluids, and their demonstration either by culture or by guinea-pig inoculation is a matter of chance. It has been shown by Eichorst (1898) that the chances of obtaining a positive result depend on the volume of fluid used. While it may thus be said that the recovery of tubercle bacilli from a fluid is strong evidence of its tuberculous origin, failure to do so is of little significance.

Pulmonary tuberculosis Evidence of pulmonary tuberculosis was obtained in 13 of the 16 cases, in 10 during life. In Case 29 a soft shadow 2.5 cm in diameter developed in the right mid-zone, five years later this was stated to have healed and left no trace. A large soft mid-zone shadow was also found in Case 24. Case 20 had a soft mid-zone shadow four months and haemoptysis 15 months after the onset of symptoms, and a miliary spread on post-mortem examination. In Case 28, six years after the onset, X-ray showed a calcified focus in the right upper zone with calcification of the tracheo-bronchial lymph-nodes. X-ray evidence of bilateral active infiltration was obtained in Case 17, 18 months after the onset and eight months before death, and in Case 30, three years after the onset. In Case 21 the sputum contained tubercle bacilli intermittently from the second year of the disease. Case 22 had haemoptysis at the onset of the illness, and 18 months later radiological evidence of pulmonary

accompanied by evidence of lymphnode enlargement or healing with calcification. It seems to us extremely probable that tuberculous polyserositis occurs in those cases in which primary infection is followed by haematogenous dissemination of bacilli, and the serous membranes are the main seat of metastatic tuberculous infection, but it is by no means clear to us why the serous membranes should be so heavily involved in some cases and not in others, nor is it clear why the disease should affect male so much more frequently than female patients.

Course of tuberculous pericarditis So far as the course of the pericarditis itself is concerned, it seems to be immaterial whether or not the other serous cavities are also involved. Both groups of tuberculous pericarditis will therefore be considered together. All the cases that we saw during the stage of pericardial effusion showed a grossly raised venous pressure and enlargement of the liver. The circulatory effects of pericardial effusion are thus not unlike those of constrictive pericarditis (Fletcher, 1945). As the effusion was absorbed and the disease passed into the stage of fibrocaseous tuberculosis of the pericardium, and finally into that of healed tuberculosis, we never saw the venous pressure fall to normal, or the liver return to normal size. Sixteen of our 18 cases of tuberculous pericarditis, four without and 14 with tuberculosis of other serous cavities, developed signs of constrictive pericarditis. In those first seen during the phase of effusion, the signs changed gradually from those of pericarditis with effusion to those of constrictive pericarditis, as the dimensions of cardiac dullness and of the cardiac silhouette shrank to more or less normal proportions. It was the rule for the transverse diameter to be a little increased at all levels, due no doubt to the thick pericardium. Pulsation of the borders of the silhouette was reduced or absent. Here the signs remained stable during the period of our observation, or until pericardectomy was performed. In Case 30, after absorption of the effusion, venous congestion and liver enlargement continued to be conspicuous five years from the onset of pericarditis, but at that time there was no ascites, oedema, or pleural effusion, and no dyspnoea, though it should be added that the patient was not fully active. This case illustrated that the healing of tuberculous pericarditis may lead to what may be termed 'latent constrictive pericarditis', a stage in which there is in fact constriction with elevated venous pressure, but no symptoms. In most of the cases of our series, high venous pressure was accompanied by ascites, oedema, and pleural effusions.

The indications for and results of pericardectomy in tuberculous pericarditis In those cases of tuberculous pericarditis developing constrictive pericarditis, the question repeatedly arose as to whether fluid in pleural or peritoneal cavities represented the effect of pericardial constriction or active tuberculous infection. A second and closely related problem concerned the stage of healing of the tuberculous process in the pericardium. Would the surgeon encounter an active tuberculous process and, if he disturbed it, would he produce a local or haematogenous spread of the disease? In patients expected to have active tuberculosis, we originally operated only if the consequences of pericardial constriction were

oedema. The condition then becomes stabilized for some months, and in favourable cases the fever gradually declines. The pericardial effusion gradually subsides, and as a rule, in two to 20 months the cardio-pericardial shadow and dullness have regressed to a size approximating to the normal, but the venous pressure remains high, the liver large, and ascites and pleural effusions persist. In less favourable cases the temperature does not settle to normal or, after a normal period, rises again with evidence of a new focus of tuberculosis. In many cases there is a steady decline in strength, and death from miliary spread, with or without the manifestations of tuberculous meningitis.

Outcome. Of the 16 patients, 11 are dead after an illness lasting from four months to five and a half years (average duration two years). One of these patients died two days after pericardectomy, the remainder as a result of widespread tuberculosis. Of the five patients alive, four (Cases 21, 27, 29, and 31) are well enough to be out of hospital, but not to work, and the fifth still receives institutional treatment 18 months from the onset. No further comment is needed to indicate the serious nature of the disease.

Pathology. The spread of tuberculosis to four serous membranes simultaneously or successively may conceivably happen in three ways. Firstly, the bacilli may spread directly from one membrane to another by invading the intervening tissue. It seems that malignant cells may spread in this way from cavity to cavity, as in the cases of malignant polyserositis referred to later in the present paper. It also seems that tuberculous pericarditis unaccompanied by pleurisy or peritonitis may arise from rupture of a caseous mediastinal lymphnode into the pericardium (Osler, 1893, Riesman, 1901, Norris, 1904), and that tuberculous pleurisy may result from either a reaction to, or in some instances a spread from, a subpleural tuberculous focus, but direct spread of tuberculosis from one cavity to another has never been observed. Nor have we found any anatomical evidence of connexions existing between pericardium, pleura, and peritoneum, there has been no instance where air replacement of a serous effusion has led to the presence of gas in an adjacent cavity. Secondly, tuberculosis might spread from one cavity to another through the lymphatics. This is unlikely because tuberculous pleurisy is usually a single lesion, and because polyserositis commonly involves not only adjacent cavities but three or four together. The third possible method, namely, the separate involvement of the serous cavities by haematogenous spread, seems the most probable for the following reasons. In 11 of the 16 tuberculous cases, foci occurred in other organs besides the serous cavities and lungs, and although in some instances (Cases 16, 18, 20, 22, 25, and 26) the manifestations of haematogenous spread occurred late and led to a fatal issue, in others (Cases 17, 29, and 30) the involvement of organs was present early in the illness, at the time when the serous membranes were being successively affected. Usually the reactions of the serous membranes to the infection were the earliest and clinically the most striking. In agreement with this conception of the pathogenesis of tuberculous polyserositis is the frequency of a pulmonary lesion of the primary type. In at least four cases the earliest lung lesion was a large rounded shadow, either

obviously endangering life, for we regarded interference with active tuberculous tissue as a dangerous procedure. Since our experience has been considerably at variance with our expectations, it is summarized in Table VII.

Unoperated patients, all with polyserositis, numbered nine, excluding the two cases of polyserositis without clinical pericarditis. Of these, seven are dead after periods of seven months to five and a half years, of the two survivors, one has had tuberculous cervical lymphnodes and caries of the tibia, in the other (Case 31) tuberculosis was never proved and constrictive pericarditis did not develop. Most of these nine were obviously suffering from widespread active tuberculosis, and operation was never considered.

Nine patients were operated on, four without and five with tuberculous infection of other serous cavities. In Case 21, three and a half years from the onset, no trace of the original tuberculous lesion was found at operation, the pericardium resected being thick scar tissue only. In the remaining cases active tuberculosis was encountered, notably in Case 13, 10 months and again five and a half years after the beginning of pericarditis. It is clear that the rate of healing of tuberculous pericarditis is slow and that it varies from case to case. On reconsidering our experience we cannot suggest how it may be possible to decide without operation whether or not the lesion is healed, temperature was always, and sedimentation rate usually, within normal limits in our cases. Our experience suggests that the dangers of interference with clinically active tuberculous tissue in the pericardium have been exaggerated. Thus of our nine operated patients three died—one, the only case without oedema and ascites, during induction of anaesthesia, another, a boy of 11 years who had been severely oedematous for months, three days after operation, the third was extremely ill before his operation and died soon afterwards. Of the six patients who survived operation, only two subsequently developed symptoms attributable to tuberculosis elsewhere, in Case 13 a tuberculous abscess of the thigh appeared three years after the first operation, in Case 24 tuberculosis of the left knee-joint, suspected at the onset of her polyserositis, became definite two months after pericardectomy. In view of the frequency with which apparently new tuberculous foci declared themselves in our patients with tuberculous polyserositis, it seems extremely doubtful whether operation ever occasioned a new haematogenous spread. On the other hand, it was not uncommon for patients to have slight or moderate pyrexia for a few days or weeks after operation. The success of the operation was unquestioned in six survivors. Ascites, oedema, and pleural effusions disappeared entirely or became less. In Case 13 the benefit from the first operation was doubtful, but that of the second dramatic.

We may sum up our views concerning indications for pericardectomy in tuberculous pericarditis as follows. Firstly, we believe that it is unwise to operate on a patient with fever, although we have never done so. Secondly, we believe that the risk of fatal dissemination of tuberculosis by excising active tuberculous tissue from the pericardium has been overrated. The risk of death from widespread tuberculosis is very great in tuberculous polyserositis treated

pressure normal. X-rays a month later revealed that the heart shadow was reduced in size. Four years later venous congestion was absent and the heart size and pulsation were normal clinically and radiologically.

Thus, neither of these patients developed constrictive pericarditis during the four years that they were observed.

Acute Idiopathic Pericarditis

In the preceding cases of acute pericarditis, proof of causation was obtained by bacteriology, operation, or autopsy in most cases, in the remainder the evidence was strong, but in one patient (Case 34), a man of 31 years who had pericarditis with a blood-stained effusion after an acute tonsillitis, classification was not possible. The pericardial fluid was sterile, and the illness was of short duration and not followed by constriction. This case may have been one of acute idiopathic pericarditis, but as the patient had been treated with penicillin and sulphonamides, sepsis cannot be excluded, nor can rheumatism or tuberculosis. In fact, we are doubtful whether the idiopathic pericarditis encountered in this country represents a distinct entity or entities. We think that it more probably includes cases which belong to one of the recognized categories, but in which identification is difficult or impossible. For this reason we doubt whether idiopathic pericarditis merits serious consideration as a cause of constrictive pericarditis.

The Cause of Constrictive Pericarditis

Reasons have already been given for believing that constrictive pericarditis must be due to antecedent tuberculous, septic, or idiopathic pericarditis. That some cases are of tuberculous origin is suggested by the early case reports. Thus Chevers's (1842) first case had tuberculosis of the cerebellum, and his fourth cases of the hip joint. Pick's (1896) third case was tuberculous. Osler (1893), describing 17 cases of tuberculous pericarditis, pointed out that patients who survived frequently developed a chronic adhesive form which might persist for years till they died from cardiac decompensation. Riesman (1901) recognized that the chronic form of tuberculous pericarditis was clinically different from the rheumatic, and that it presented the features of the condition described by Pick. That tuberculous pericarditis in healing frequently leads to constrictive pericarditis was also the experience of Blalock and Levy (1937) and Keefer (1937). On the other hand, Harvey and Whitehill (1937), analysing 95 cases of tuberculous pericarditis that occurred over 45 years at the Johns Hopkins Hospital, stated 'we have never seen a patient who recovered from the active process develop chronic constrictive pericarditis with the syndrome of in-flow stasis'. Again, Wells (1901) found 10 cases of tuberculous pericarditis in 1,048 autopsies, but no case of Pick's disease amongst them, he regarded calcification of the pericardium as rarely tuberculous in origin. Smith and Willius (1932), in an analysis of 114 cases of adherent pericardium sectioned at the Mayo Clinic, found no evidence of tuberculosis in any of 15 cases of

by conservative means, and in our experience has not been increased by operation. The real objection to resecting active tuberculous tissue from the pericardium is that, as in Case 13, there may be further exudation, which may later become organized into dense connective tissue over the resected area. This risk probably diminishes with time. It is, therefore, wise to delay operation as long as possible, simply to make surgery more satisfactory. Delay may, however, be dangerous when constriction of the heart is severe, for example, Case 23 undoubtedly deteriorated in the months before operation, and might have survived earlier intervention. Our earlier views as to the dangers of surgery in active tuberculous pericarditis were similar to those expressed some years ago by Churchill (1930) and Keofer (1937), our later views, determined by experience, correspond to those of Blalock and Levy (1937).

Acute Septic Pericarditis

In five patients under our observation, acute septic pericarditis occurred as a terminal complication respectively of osteomyelitis, meningococcal meningitis, lung abscess and empyema, suppurative pneumonitis, and pneumonectomy for carcinoma of bronchus. All the patients died before chronic pericardial thickening could occur, and require no further consideration here. The two following patients with septic pericarditis recovered.

Case 32 A captain, aged 34 years, received a gunshot wound of the right leg in March, 1943, followed by septic arthritis in the right knee, staphylococcal septicæmia, left empyema, septic pericarditis, and left panophthalmitis. He was treated with penicillin, drainage of the pericardium, rib-resection, and removal of the eye, and recovered. He subsequently developed necrosis of costal cartilages, for which he was admitted to our care in December, 1943. The necrotic costal cartilages were excised. The pericardial sinus had then closed, and there were no signs of constrictive pericarditis. When last seen (November, 1946), he was quite well, the venous pressure was normal, and the cardiac pulsations free.

Case 33 A captain in the Home Guard, aged 44 years, in October, 1942, was standing two and a half feet from a hand-grenade when it exploded, he fell riddled with metal. Five hours later he was seen by one of us (T. H. S.) and was found to have multiple wounds, including a left hæmothorax, possibly a hæmopericardium, and a rigid belly, two small holes in the jejunum were sutured and 500 c.c. of blood aspirated from the left side of the chest. Pericardial aspiration was negative. Nine days later he was transferred to Harefield Hospital (November 3). He had two puncture wounds in the anterior part of the chest, below the left clavicle and 2 cm. internal to the left nipple, and X-rays revealed a metallic foreign body situated posteriorly in the left side of the chest, a left hæmothorax, and an enlarged cardiac shadow suggestive of pericardial effusion. A week later (November 10) the venous pressure was raised to 10 cm., and a pericardial friction rub was heard over the whole precordium. Next day the heart shadow was further increased in size and the rub was louder, but the venous pressure had decreased to 5 cm. The pyrexia, which he had had since admission and which reached 104° F. on November 13, fell to normal on November 15, after 28 gm. of sulphadiazine had been given. By November 19 the pericardial rub was no longer audible and the venous

affection is usually overlooked clinically' A tuberculous origin is also supported by a past history of pleurisy in three cases (compare Case 14 diagnosed as pleurisy until X-ray examination) and haemoptysis in two Age and sex incidence are also in conformity The 18 cases of acute tuberculous pericarditis, with or without polyserositis, ranged in age from four to 49 years, and averaged 19 years, the 11 cases of chronic constrictive pericarditis ranged from 18 to 63 years, and averaged 46 years In various series of six or more cases of constrictive pericarditis which have been reported from this country and the United States of America, male patients have predominated, the total figures, including the present series, are 68 male and 30 female The male preponderance in acute tuberculous pericarditis has already been noted The conclusion that tuberculosis is the cause of the vast majority, if not all, of cases of constrictive pericarditis is supported by our experience of the end results of tuberculous and septic pericarditis Thus, 14 of 16 cases of proved or suspected tuberculous pericarditis in healing passed into the constrictive form, and the two exceptional cases were not proved to be tuberculous It is true that most of these cases had advanced only to the fibrocaseous stage when proof was obtained, but in Case 21, with proved tuberculous polyserositis, the pericardium at operation showed fibrosis only, with no trace of the original infection On the other hand, in our two surviving cases of septic pericarditis, one proved and the other suspected, constrictive pericarditis did not develop subsequently

The idea that constrictive pericarditis may represent the healed stage of a distinct idiopathic pericarditis receives no support from past writing or from the cases reported here It is doubtful whether idiopathic pericarditis as seen in this country comprises any form distinct from those named on page 299 The only case so classified in our series did not develop constrictive pericarditis

Polyserositis

Many of the cases here reported had fluid in the great serous cavities In order to make the position of the cases clear it is necessary now to consider briefly polyserositis, a term over which there is still much confusion We consider that the use of this term should be restricted to conditions in which inflammation affects two or more of the great serous cavities, and should not be used for collections of fluid that are believed to be transudates Polyserositis is never used to describe the transudates of nephritis or cardiac failure, but it is still used wrongly as a synonym for constrictive pericarditis or Pick's disease, in which the collections of fluid in the serous cavities are not inflammatory in origin This misuse of the term has probably arisen in two ways Thus, a true polyserositis of tuberculous origin in which the effusions are inflammatory may, in healing, develop into a constrictive pericarditis where the effusions are a consequence of cardiac constriction and disappear after the pericardium is excised In these cases it is beyond our competence to say exactly where polyserositis ends and constrictive pericarditis begins The second reason for

calcified pericardium The series of Harvey and Whitehill (1937), Wells (1901), and Smith and Williams (1932) suffer from being analyses of case or autopsy records, their conclusions are thus dependent on observations and records not made to test any specific hypothesis

That septic pericarditis may give rise in healing to constrictive pericarditis is a view widely held, but the evidence is far from conclusive We have been unable to find any case report in which a proved septic pericarditis later developed chronic constrictive pericarditis in the healed phase Burwell and Flickinger (1935) described the case of a 17-year-old negro with a two weeks' history of fever and dyspnoea who presented fever, tachycardia, venous congestion, ascites, and bilateral pleural effusions, and in whom fluoroscopy showed a poorly pulsating heart, operation disclosed a pericardium 7 mm thick containing encapsulated pus from which *Staphylococcus aureus* was grown One of our fatal cases of septic pericarditis was very similar It is to be noted that these are not strictly cases of chronic constrictive pericarditis, but rather cases in the late acute or subacute phase Most of the case reports in which a septic origin is claimed (Nigst, 1934, White, 1935) are similar to our Case 11 in which double pneumonia at the age of 30 years was followed by empyema and rib-resection During convalescence the patient's temperature rose, his legs swelled, and he noticed distension of the veins in his neck, he was told that he had a heart complication and put to bed He recovered, but the oedema recurred four years later, and was followed by ascites, both becoming gross Pericardectomy was performed at the age of 43 years, and both ascites and oedema disappeared The pericardium showed fibrous tissue without calcification, and with no evidence as to the original infection In this case it is possible that the empyema was complicated by a suppurative pericarditis which subsided, leaving fibrous tissue, the contraction of which led to the onset of oedema four years later, but the fallacy of such argument is shown by Case 15, where a pyococcal origin seemed equally certain and operation disclosed active tuberculosis Recent American series differ in the importance attached to sepsis and tuberculosis as causes of constrictive pericarditis Thus, Beck (1937) considered that most cases were due to sepsis and about 10 per cent to tuberculosis On the other hand, Blalock and Burwell (1941) ascribed 18 of their 28 cases to tuberculosis and three to sepsis, but tuberculosis was suspected to be the cause in several others Harrison and White (1942) gave tuberculosis as the cause in five, sepsis in one, and an unknown cause in 31 cases

We may turn now to the evidence provided by our own cases We interpret the past history as being in favour of tuberculosis as a cause In 10 of our 11 cases of constrictive pericarditis the past history is chiefly remarkable in revealing no illness that could be construed as an acute pericarditis It seems clear, therefore, that the preceding acute pericarditis must have given rise to an illness so vague and ill-defined that it was not diagnosed, and did not immobilize the patient for long In our experience only tuberculous pericarditis is likely to be unrecognized in this way Osler stated in 1893 'Tuberculosis follows hard upon rheumatic fever as a cause of pericarditis', and 'The

in the fluids, are usually diagnostic. The differentiation between polyserositis of tuberculous origin and constrictive pericarditis, on the other hand, may be very difficult, for in each the outstanding features are collections of fluid in the pleurae and peritoneum, while oedema, liver enlargement, and venous engorgement are found not only in constrictive pericarditis, but in polyserositis when the pericardium is involved. Tuberculous polyserositis is most easily recognized soon after its onset. The appearance of a straw-coloured effusion in one serous cavity, quickly followed by fluid in another, associated with moderate or high fever with considerable subjective disturbance, is characteristic. It is not always possible to recover tubercle bacilli from the fluids, but other tuberculous lesions, particularly of the primary type in the lung, are common. In tuberculous pericarditis without infection of the other serous cavities the fever is shorter and lower, subjective disturbance is less, and pleural and peritoneal effusions never occur in the absence of venous congestion in the neck and considerable enlargement of the liver. A pericardial rub or signs of a pericardial effusion are usual. The importance of X-ray screening cannot be exaggerated. In constrictive pericarditis fever is absent throughout, unless intercurrent pyrexial illness occurs, signs of acute pericarditis, such as a pericardial rub or the characteristic dullness of effusion, are never found. However, the differentiation between healing active tuberculous and chronic constrictive pericarditis may be impossible, as in our Cases 12 and 15. As has been pointed out earlier, the protein content of pleural and peritoneal effusions is no guide as to whether the serous membranes are the seat of tuberculosis. Nor can the failure to find tubercle bacilli be relied on to exclude tuberculous infection. In brief, the decision as to whether the patient is suffering from tuberculous pericarditis, tuberculous polyserositis, or chronic constrictive pericarditis is usually not difficult in the early stages, when the clinical pictures are distinct. Later the diagnosis may be difficult, for then the dominant lesion in all is the compression of the heart.

Summary

1 Constrictive pericarditis is a clinical entity which should be differentiated from other forms of adherent pericardium and from polyserositis. Ascites and oedema are its chief symptoms; venous congestion and enlarged liver are the chief physical findings. The heart itself exhibits little abnormality. The pericardium is thick and fibrous, sometimes calcified, and usually reveals no clue as to the nature of the causative disease.

2 Constrictive pericarditis is not due to antecedent acute pericarditis arising from the following processes—rheumatism, uraemia, myocardial infarction, or malignant metastasis. During a seven-year period all cases of other forms of acute pericarditis, namely, tuberculous, septic, and so-called idiopathic, have been collected and followed.

3 Eighteen cases of acute tuberculous pericarditis have been studied. In four, no other serous cavity appeared to be infected. In 14, pericarditis was part of a tuberculous polyserositis.

the confusion is the occurrence of chronic hyperplastic peritonitis, in which thick layers of white material are laid down over the liver (*Zuckergussleber* of Curschmann), spleen, and intestines. Pick (1896) suggested that this condition was due to a chronic infection by organisms of low virulence introduced into the peritoneum during paracentesis, and cited cases in which the abdomen had been tapped 10, 15, and 301 times. According to Borrmann (1927) and Cooke (1919) the intestines may be involved even when ascites has never existed, in Hale White's (1908) two cases, where perihepatitis existed without chronic peritonitis, ascites had been absent. Yet in most cases hyperplastic peritonitis occurs in association with long-lasting ascites that has been frequently tapped. Moreover, the cause of ascites is not always the same. Thus Blalock and Burwell (1935) found hyperplastic peritonitis in dogs in which constrictive pericarditis had been produced experimentally by the injection of aleuronat into the pericardium. Hyperplastic peritonitis has also occurred with ascites due to constrictive pericarditis, as has been described by Pick (1896) and Flick and Gibbon (1934). In 19 of the 22 cases collected by Hale White (1908) the kidneys were granular, in these, hyperplastic peritonitis was grafted on to the ascites of nephritis. In yet other instances it may complicate cirrhosis of the liver (Fagge, 1875).

It is not difficult to understand how the occurrence of hyperplastic peritonitis has led to the confusion of constrictive pericarditis and polyserositis. Before its physical signs were widely known, constrictive pericarditis was diagnosed only *post mortem*, and then usually in patients in whom the abdomen had been tapped frequently and in whom hyperplastic peritonitis is not uncommon. It is not unnatural that the thick coatings of the heart and abdominal organs should have been attributed to a common cause, and the diagnosis of polyserositis made. Now that we know that ascites is actually a consequence of the pericardial lesion, and that hyperplastic peritonitis is usually a complication of ascites, the reason for confusion with polyserositis has gone. Restricting the term polyserositis to its proper usage, we may now consider briefly its causes, other than tuberculosis, as we have experienced them in this seven-year period, and its diagnosis from constrictive pericarditis.

Causes of polyserositis other than tuberculosis. Occasionally pyogenic organisms may affect more than one serous cavity. In Great Britain the next commonest cause of polyserositis after tuberculosis is malignant metastasis. While collecting the material for the present paper, we have encountered four cases of polyserositis due to this cause. In two cases the growth originated in the ovary, in Case 34, ascites was followed by left and, later, right pleural effusion, while in Case 35 ascites and oedema were followed by left pleural effusion. In two cases the growth originated in the bronchus, in Cases 36 and 37 pleural effusion was followed by pericardial effusion. Other sites are known for the primary growth.

The diagnosis of polyserositis and constrictive pericarditis. The diagnosis of polyserositis of malignant or septic origin seldom presents difficulty, as the symptoms and signs of the primary lesion, as well as the characters of the cells

in the fluids, are usually diagnostic. The differentiation between polyserositis of tuberculous origin and constrictive pericarditis, on the other hand, may be very difficult, for in each the outstanding features are collections of fluid in the pleurae and peritoneum, while oedema, liver enlargement, and venous engorgement are found not only in constrictive pericarditis, but in polyserositis when the pericardium is involved. Tuberculous polyserositis is most easily recognized soon after its onset. The appearance of a straw-coloured effusion in one serous cavity, quickly followed by fluid in another, associated with moderate or high fever with considerable subjective disturbance, is characteristic. It is not always possible to recover tubercle bacilli from the fluids, but other tuberculous lesions, particularly of the primary type in the lung, are common. In tuberculous pericarditis without infection of the other serous cavities the fever is shorter and lower, subjective disturbance is less, and pleural and peritoneal effusions never occur in the absence of venous congestion in the neck and considerable enlargement of the liver. A pericardial rub or signs of a pericardial effusion are usual. The importance of X-ray screening cannot be exaggerated. In constrictive pericarditis fever is absent throughout, unless intercurrent pyrexial illness occurs, signs of acute pericarditis, such as a pericardial rub or the characteristic dullness of effusion, are never found. However, the differentiation between healing active tuberculous and chronic constrictive pericarditis may be impossible, as in our Cases 12 and 15. As has been pointed out earlier, the protein content of pleural and peritoneal effusions is no guide as to whether the serous membranes are the seat of tuberculosis. Nor can the failure to find tubercle bacilli be relied on to exclude tuberculous infection. In brief, the decision as to whether the patient is suffering from tuberculous pericarditis, tuberculous polyserositis, or chronic constrictive pericarditis is usually not difficult in the early stages, when the clinical pictures are distinct. Later the diagnosis may be difficult, for then the dominant lesion in all is the compression of the heart.

Summary

1 Constrictive pericarditis is a clinical entity which should be differentiated from other forms of adherent pericardium and from polyserositis. Asites and oedema are its chief symptoms, venous congestion and enlarged liver are the chief physical findings. The heart itself exhibits little abnormality. The pericardium is thick and fibrous, sometimes calcified, and usually reveals no clue as to the nature of the causative disease.

2 Constrictive pericarditis is not due to antecedent acute pericarditis arising from the following processes—rheumatism, uraemia, myocardial infarction, or malignant metastasis. During a seven-year period all cases of other forms of acute pericarditis, namely, tuberculous, septic, and so-called idiopathic, have been collected and followed.

3 Eighteen cases of acute tuberculous pericarditis have been studied. In four, no other serous cavity appeared to be infected. In 14, pericarditis was part of a tuberculous polyserositis.

4 Of the four cases of acute tuberculous pericarditis not associated with polyserositis, only two, both with effusion, were diagnosed before operation. Two were cases previously diagnosed as constrictive pericarditis, and were found to have active tuberculous pericarditis at operation. Acute tuberculous pericarditis may easily be overlooked clinically.

5 Of 16 patients suffering from tuberculous polyserositis (including two with no clinical pericarditis), 11 are dead after being ill on an average for two years and seven months. Four are well enough to be out of hospital, and one still receives institutional treatment 18 months from the onset. Pulmonary tuberculosis, specially of the primary type, is usual, other tuberculous lesions are common, and death is often due to miliary spread.

6 Of 18 patients suffering from acute tuberculous pericarditis, four without and 14 with tuberculosis of other serous cavities, 16 developed constrictive pericarditis. Pericardectomy was performed in nine of these cases, of whom three died; the remaining six improved greatly. The pericardium showed a healed scar in one, active tuberculosis in seven, seven months to five and a half years from the onset. Pericardectomy in the presence of active tuberculosis does not seem to increase the liability to dissemination of the disease.

7 Of seven patients with acute septic pericarditis, five died in the acute phase. Neither of the two survivors developed constrictive pericarditis.

8 One case of so-called idiopathic pericarditis did not develop constrictive pericarditis.

9 It is concluded that in Great Britain most, and perhaps all, cases of constrictive pericarditis are due to antecedent acute tuberculous pericarditis, because (a) it is the rule for constrictive pericarditis to develop as tuberculous pericarditis heals, and no other form of acute pericarditis has been observed to heal in this way, and (b) in chronic constrictive pericarditis it is the rule for there to be no past history of acute pericarditis. Of all the forms of acute pericarditis, that due to tuberculosis is by far the most likely to be overlooked.

Our thanks are due to Dr K R Stokes, Dr W D W Brooks, Dr E I Jones, Mr Vernon Thompson, and Mr A Dickson Wright for permission to report cases under their care, to Professor W D Newcomb, Dr D M Pryce, and Dr E Nassau for the pathological reports, to Dr L G Blair and Dr E Rohan Williams for the X-ray reports, and to Mr A W Holder and Mr N W Pereira for the photographs.

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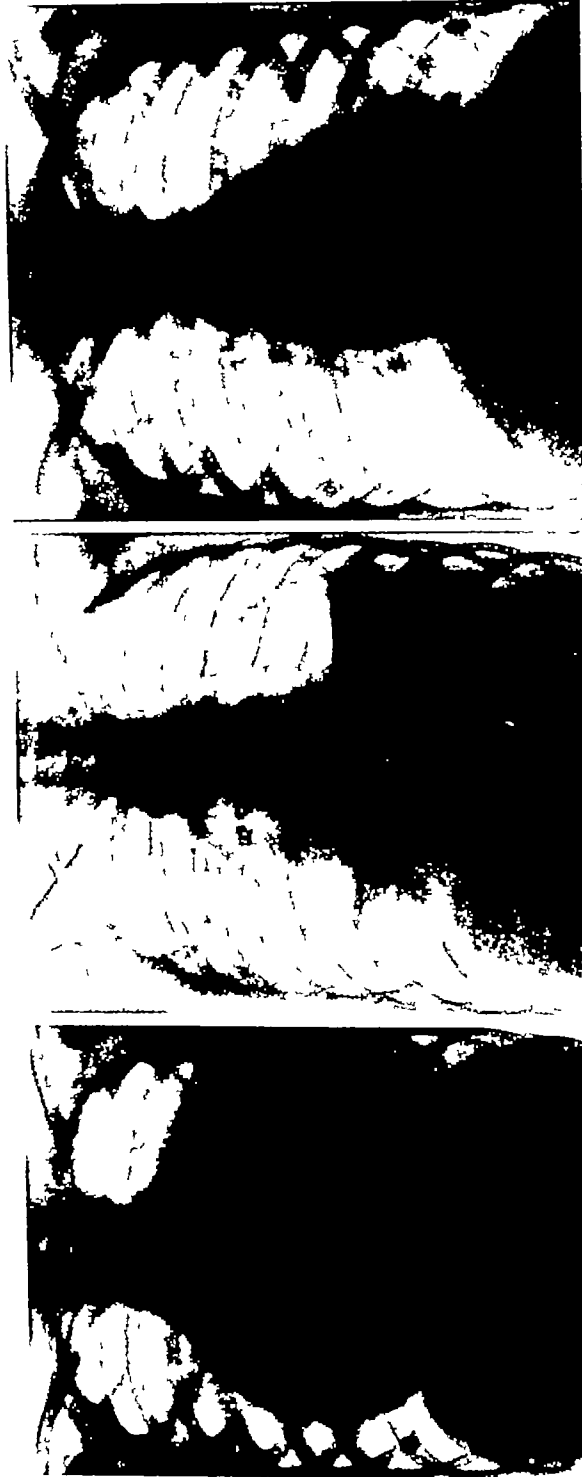


FIG. 1 Case 13 X ray of chest on admission in October, 1941, showing large pericardial effusion

FIG. 2 Case 13 X ray after aspiration of pericardial fluid, and air replacement showing thickened pericardium (December, 1941)

FIG. 3 Case 13 X ray after first pericardectomy and after absorption of left post operative pleural effusion, showing normal heart size (May, 1942)



FIG 5 Case 13 Right lung field in August, 1947, after second pericardectomy, showing calcified focus in mid zone



FIG 4 Case 13 Right lung field in January, 1942, before first pericardectomy, showing active tuberculous focus in mid zone

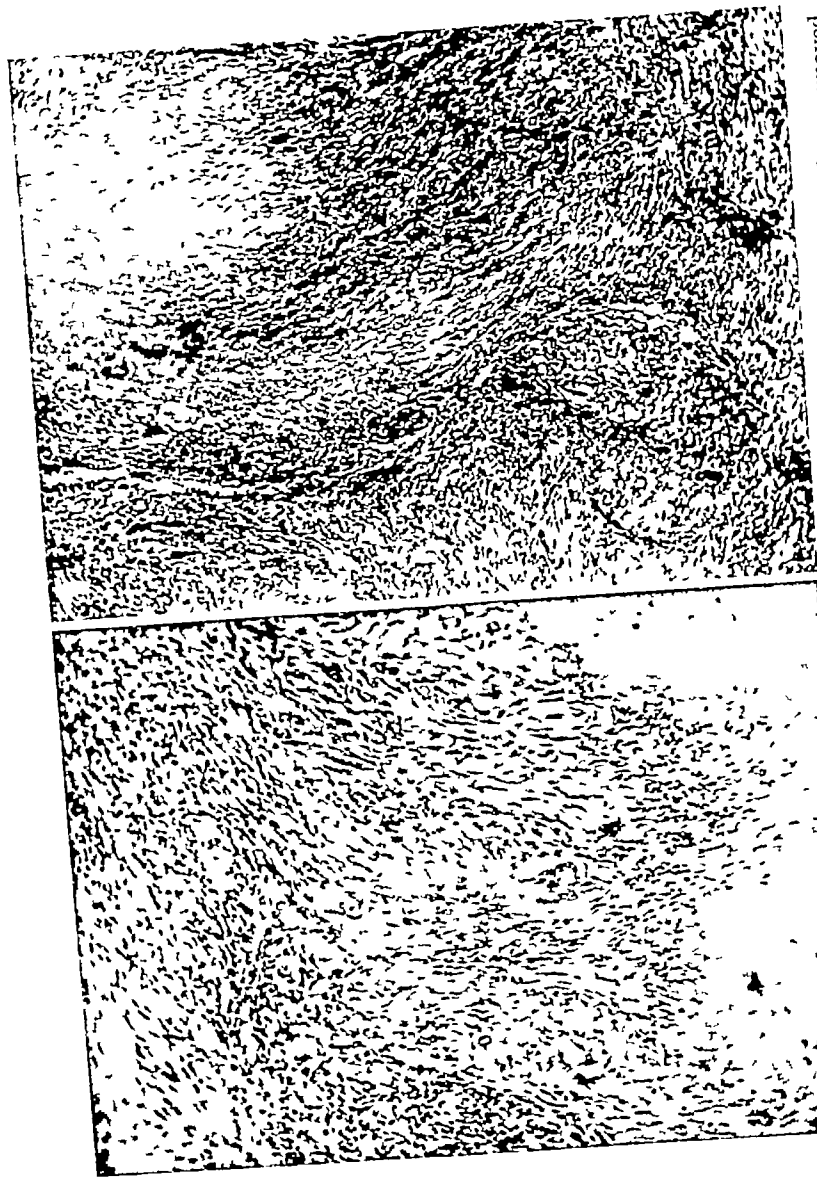


FIG 6 Case 13 Section of pericardium removed at first operation in April, 1942, showing active tuberculous tissue ($\times 100$)

FIG 7 Case 13 Section of pericardium removed at second operation in November, 1946, showing that the tuberculous process was still active though chronic ($\times 45$)

THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1948

FORTY-SECOND ANNUAL GENERAL MEETING

THE FORTY-SECOND ANNUAL GENERAL MEETING was held at Liverpool on Friday and Saturday, May 14 and 15, in the Medical Institute, Mount Pleasant. The attendance book was signed by 181 members and 11 visitors. The proceedings began at 10 a.m.

The President, Dr A. Greig Anderson, was in the Chair.

The Minutes of the last Annual General Meeting, having been published in the Quarterly Journal of Medicine, were taken as read, confirmed, and signed.

The Treasurer presented the Annual Accounts. The year had started with a bank balance of £581, £300 had been invested in the Post Office Savings Bank, and the closing balance was £416. The Treasurer pointed out that there had been no increase in subscriptions since the war and that the circulation of the *Journal* had gone up from 850 before the war to 1,100. He felt, therefore, that the position both of the Association and the *Journal* was very satisfactory. On the proposal of the Treasurer, seconded by the Secretary, the Accounts were accepted and entered in the Minutes.

Joint Meeting with the Association of American Physicians. The Secretary read a letter from Dr Henry N. Thomas, the Secretary of the American Association, stating that he thought that in view of the circumstances in England, the Joint Meeting would be impracticable in 1948, and pointed out that the proposal for the Joint Meeting, though deferred, had not been dropped.

Travelling Expenses for Members of the Committee. On the proposal of the Secretary, seconded by the Treasurer, it was agreed that first class travelling expenses should, in future, be paid to members attending Committee Meetings.

Place of Meeting in 1949. It was agreed to accept with gratitude the invitation to meet in Belfast in 1949, and the Secretary reported invitations which suggested the probability that the Association would meet in 1950 in London, in 1951 at Glasgow, in 1952 at Sheffield, in 1953 at Newcastle, and in 1954 at Dublin.

Election of Officers

President. Professor John Hay was elected President and took the Chair. He expressed the thanks of the Association to the retiring President, Dr A. Greig Anderson.

Executive Committee

President. Professor John Hay

Treasurer. Dr C. Newman

Secretary. Dr W. I. Card.

Members for England

Dr D. Evan Bedford

Dr E. Bulmer

Dr Robert Coope

Professor C. H. Stuart-Harris

Dr G. Bourne

Dr T. C. Hunt

Members for Scotland

Dr J. N. Cruickshank

Dr T. N. Morgan

Dr J. K. Slater

Members for Ireland

Dr T. H. Crozier

Dr D. M. Mitchell

Dr A. Thompson

Election of Honorary Member

Dr A Greig Anderson

Election of Extra Ordinary Members

Dr D. K. Adams.
 Dr F. M. B. Allen
 Dr. N. Capon
 Dr H. Wallace-Jones
 Dr. H. MacLean
 Professor F. J. Nattrass
 Dr. R. A. Rowlands
 Sir Charles Symonds

Election of Ordinary Members

Eric George Laphorne Bywaters, M D, F R C P, Director, Rheumatism Research Dept., Canadian Red Cross Hospital, Taplow
 Sheila Callender, M D, M R C P, May Reader in Medicine, Oxford
 Cyril Astley Clarke, M D, M R C P, Assistant Physician, Royal Liverpool United Hospital
 William Trevor Cooke, M D, F R C P, Reader in Medicine, University of Birmingham.
 Thomas Neilson Fraser, M D, M R C P, Assistant to Regius Professor of Medicine, Glasgow University
 Hugh Gregory Garland, M D, F R C P, Physician, Leeds General Infirmary
 George Dickinson Hadley, M D, F R C P, Director, Dept of Medicine, Canadian Red Cross Hospital, Taplow
 John Locke Lovibond, M D, F R C P, Assistant Physician, Westminster Hospital
 L. Kevin Malley, M D, Physician to Out-patients, Mater Misericordiae Hospital, Dublin
 Neville Oswald, M D, F R C P, Assistant Physician, St Bartholomew's Hospital
 George Algernon Smart, M D, M R C P, Assistant Physician, Bristol Royal Hospital
 Robert William Magill Strain, M D, Lecturer in Medicine, Queen's University, Belfast

Election of Editors

Professor D. M. Dunlop
 Professor R. Platt

The President, on behalf of the Association, thanked Professor A. W. M. Ellis and Professor J. W. McNee for their many years of valuable service as editors, and Professor L. J. Witts, on his retirement, for his many years of valuable service to the Association both as Secretary and Treasurer.

SCIENTIFIC BUSINESS

Friday Morning, May 14

1 Dr W. RITCHIE RUSSELL describing *The Pre paralytic Stage of Poliomyelitis* pointed out that early diagnosis of poliomyelitis is important, as rest from the onset of the pre-paralytic phase greatly reduces the danger of severe paralysis. In 100 convalescent cases old enough to question, all had pre-paralytic symptoms, which in 89 per cent were abrupt in onset. Forty eight per cent had a prodromal illness. Eighty four per cent had pains, slight or severe, in the neck, spine, chest, abdomen, or limbs, and poliomyelitis without pain is exceptional. When the pre-paralytic phase began abruptly, paralysis appeared within four days in 76 per cent of cases. In atypical cases the prodromal illness appeared to continue into the pre-paralytic stage.

Dr J. ST. C. ELKINGTON suggested that the meningeal signs were not due to actual meningeal involvement. There was a lack of correspondence between the presence of neck rigidity and pathological evidence of lesions in the meninges. Moreover, meningeal and root pains were common without any increase of cells or protein in the cerebrospinal fluid.

PROFESSOR A. A. MONCRIEFF said that during recent epidemics he had seen patients suspected of being in the pre-paralytic stage of poliomyelitis who had not developed paralysis. He also instanced the case of a child, whose parents (who were doctors) diagnosed rheumatic fever, who recovered, and seven days later the mother developed poliomyelitis with paralysis. He wondered how many cases started with pains and subsequently aborted without developing paralysis.

DR. RITCHIE RUSSELL, replying, said that he thought that the virus produced lesions in the cord which were responsible for producing the pains, but these did not necessarily produce paralysis

2 DR E G L BYWATERS, describing *A Variant Type of Rheumatoid Arthritis resembling 'Palindromic Rheumatism'*, said that recurrent transient joint pains and swelling lasting many years without radiological bony change, together with nodules and par-articular swellings, constituted the syndrome of 'palindromic rheumatism' (Hench) Such a case was described which later developed radiological changes and nodules histologically characteristic of rheumatoid arthritis A gradation towards rheumatoid arthritis was illustrated by other cases which showed the same structurally specific cutaneous nodules and transient Dupuytren-like palmar contractures as did the first case

3 DR F PARKES WEBER, with R W RAVEN and L WOODHOUSE PRICE (introduced), described the *Necrobiotic Nodules of Rheumatoid Arthritis* He said that the case on which he based his communication was that of a woman aged 62 years who developed progressive rheumatoid arthritis at 31 years, but this became quiescent In 1946 the disease flared up, with fresh nodules in various parts, and grave constitutional symptoms referable to the respiratory system, abdomen, and heart She died in 1947 Necropsy showed typical necrobiotic lesions, not only the old ones about the elbows, but in the scalp, abdominal wall, glottis, pericardium, pleurae, peritoneum, myocardium, and lungs He summarized conclusions based on the present and other cases and the modern literature

DR BYWATERS said that he had seen nodules similar to those described by Dr Parkes Weber on the apex of the heart, which were presumably due to the trauma of the heart-beat, and so corresponded to other nodules produced on sites of trauma

DR H K GOADBY described the case of a policeman aged 42 years who for 10 years had had periodical swellings of the joints, with nodules on the dorsum of the hands and feet, lasting about three days This illness had started with three haematemeses, but no cause for these had been found by exploratory operation

DR B E SCHLESINGER suggested that a palindromic course was seen not only in rheumatoid arthritis but also in rheumatic fever He had seen cases with carditis and other rheumatic manifestations which ran a palindromic course and were certainly related to acute rheumatism

DR PARKES WEBER, replying, said that he was originally against the view that rheumatoid arthritis was related to rheumatic fever, but had subsequently changed his opinion There were adult cases which fell between the two diseases Both diseases had a tendency to relapse Indeed, he thought that there was no such thing as a safely 'burnt-out' case of rheumatoid arthritis

4 DR C E DAVIES discussed the *Diagnosis of Calcified Aortic Valve* He said that aortic systolic murmurs which are not associated with aortic regurgitation, aortic dilatation, or the classical features of aortic stenosis are frequently difficult to interpret In some cases such murmurs are due to calcification of the aortic valve The diagnosis of calcified aortic valve depends on radiological demonstration of the lesion The established methods of screening and over-penetrating oblique radiographs are unsatisfactory Over-penetrating X rays do not distinguish between intracardiac and extracardiac calcification Oblique tomography of the heart in the plane of the aortic valves has been found to be far more successful The cases investigated concerned in all 12 men and two women The average age was about 50 years Ten of the patients suffered from breathlessness, angina, or syncope, eight had enlarged hearts, nine showed thrills, and all had systolic murmurs The aortic second sound was absent in 10 cases Six had soft diastolic murmurs The blood pressure was not characteristic, the electrocardiograms were not helpful, the Wassermann reaction was negative in all cases Screening showed the calcified lesion in five cases, tomography in all 14

DR R W D TURNER, who had investigated 30 cases, felt that screening with the diaphragm cut down to an aperture of one inch was a better way of making a certain diagnosis than tomography

SIR JOHN PARKINSON thought that aortic stenosis was often missed, relatively few cases were recognized clinically A harsh systolic murmur without a thrill, specially if associated with angina, should lead to suspicion He thought that tomography was a useful method, but unless the valve could be recognized as a moving shadow and distinguished from the mitral valve by radioscopy, tomography was uncertain

Dr F PARKES WEBER thought that it was occasionally possible to make the diagnosis without the use of X-rays

Dr DAVIES, replying, said that screening to some extent depended on the eye of faith. A still picture did make general agreement possible. In the presence of an effusion screening was not helpful. That tomography could be applied to the exact position of the aortic valve had been verified by tomography of the cadaver

6 Dr D K O'DONOVAN, describing a *Calcium Retention Test*, said that it was already reported that in adults who had clinical evidence of calcium deficiency, but normal serum calcium, there was a greater retention of intravenous calcium than in normal controls. The test has now been applied to the investigation of hypocalcaemic patients. They included 12 cases of hypoparathyroidism, nine who for different reasons were deficient in calcium, and three of unknown aetiology. All were given preliminary treatment with calciferol. The results indicated that hypoparathyroid patients retained little calcium in the bones (indicating saturation) whilst those with calcium deficiency retained much more. In the three cases of hypocalcaemia of unknown origin the results agreed with the hypothesis that they had idiopathic hypoparathyroidism. Examination of the histones in the light of these findings suggests that in one instance the hypoparathyroidism originated during a phase of temporary idiopathic stentorrhoea, and in another during prolonged lactation. The calcium retention test may, therefore, prove useful in the investigation of hypocalcaemia of unknown origin

PROFESSOR A A MONCRIEFF asked the size of the test dose of calcium gluconate

Dr G GRAHAM asked whether the calcium retention test had been compared with the calcium balance. He thought that the test would be valuable if they corresponded

Dr C L CORR suggested that the ability of the bones to take up calcium might influence the results, and asked whether the effect had been tried on ambulant as compared with resting patients, because the bones of a resting patient lose their avidity for calcium. He asked for further details of the excretion of calcium after the test dose

Dr D. A K BLACK asked what proportion of the test dose was accounted for in a normal patient

Dr O'DONOVAN, replying, said he employed a test dose of 1 c.c. of 10 per cent calcium gluconate per 6 lb. of body-weight. With larger doses there was a danger of toxic symptoms, but with this dose no harm was done even to a hypercalcaemic patient. He had compared the test with the calcium balance only in a limited number of cases. He had found no difference between ambulant and resting patients to suggest that the avidity of the bones affected the test in any way, but he had never done it on a patient completely immobilized in plaster. The excretion of calcium in one hour was equivalent to 20 per cent or less of the injected calcium. In hypocalcaemic cases the urinary loss was nil. Using the above test dose of calcium he had found a rise in serum level of 1 or 2 mg per 100 c.c. at the end of an hour when the subject was saturated. In calcium deficient cases the increase in serum calcium varied from zero to 0.9 mg per 100 c.c.

The Association adjourned at 12.15 p.m.

At 1.0 p.m. the members and guests lunched at the Medical Institution.

At 2.30 p.m. there was a demonstration of clinical cases in the annexe of the Radium Institute, and bacteriological, pathological, and radiological demonstrations in the Medical Institution

At 3.30 p.m. the Association was entertained to tea at the Medical Institution by the local members

4.0 p.m. Afternoon Session

1 Dr A J V CAMERON (introduced by Dr J N CRUICKSHANK) discussed *Peripheral Venous Pressure Measurements in the Assessment of Cardiac Failure*. He said that using a direct method, 450 estimations of the pressure in the arm veins were performed on 200 cases (50 normal, 100 cardiac failure, 50 miscellaneous diseases). The zero reference level was the phlebostatic plane of Burch and Winsor. Normal values ranged from 60 to 140 mm. of saline. A significant rise of the arm vein pressure in response to manual abdominal compression in cases of cardiac failure was contrasted with the absence of such a rise, or even a fall, in the normal subject and in patients with various cardiovascular lesions not accompanied by cardiac failure. It was considered that this measurement gave

additional information to that obtained from the initial venous pressure and might be even more important than the latter. Reference was made to W Pasteur who originally observed this phenomenon in the cervical veins in 1885

PROFESSOR E J WAYNE suggested that observation of the veins of the neck alone would provide all the information required and avoid the necessity of puncture

DR CAMERON, replying, pointed out that observation of the neck veins had certain disadvantages

- (1) These veins might not be visible even in the presence of venous hypertension
- (2) Full veins might be associated with a normal pressure
- (3) The abdominal compression sign could not be readily evaluated

2 DR G M WATSON and DR D G CAMERON (introduced by PROFESSOR L J WITTS) described *Experimental Macrocytic Anaemia of Intestinal Origin*. They said that attempts to reproduce pernicious anaemia in animals by resection of the stomach and intestine had been unsuccessful, but some early experiments with intestinal strictures and cul-de-sac had led to macrocytic anaemia in dogs. In the present experiments similar techniques had been applied to rats, and it was found that a macrocytic anaemia followed the formation of a blind intestinal loop. It was impossible to make reliable strictures in rats, so attention was concentrated on the production of blind intestinal loops. Loops which empty by peristalsis sometimes lead to anaemia, macrocytic anaemia invariably follows the production of a loop so arranged that peristalsis moves towards the blind end, so causing dilatation of the loop and a failure to empty. The development of anaemia depends upon distension of the loop and the longer the loop the more quickly anaemia appears. This anaemia very accurately resembles the pernicious anaemia of human beings and appears to respond to liver extracts, provided the animal is otherwise healthy and there is no pyogenic infection.

PROFESSOR WITTS said that Drs Watson and Cameron had done the whole of this experimental work. It was the first time that anything really like pernicious anaemia had been produced in animals. It was reminiscent of the cases of macrocytic anaemia which sometimes developed after the treatment of Crohn's disease by anastomosis, leaving a blind loop of intestine. The results seemed to revive the idea of intestinal toxæmia. The method would certainly be useful in the assay of liver extracts, and in determining the mechanisms responsible for the production of pernicious anaemia. At present he did not like to suggest how the blind loop acted, whether by inhibiting the haemopoietic principle, or in some other way, but he looked forward to important results in the future.

PROFESSOR L S P DAVIDSON offered his congratulations on an excellent piece of work, and said that the photographs of the blood films really had resembled those of pernicious anaemia.

DR W T COOKE asked whether the animals suffered from diarrhoea or lost weight, because blind loops of intestine tend to cause steatorrhoea, and it was possible that the anaemia might be the macrocytic anaemia of steatorrhoea and not pernicious anaemia.

DR R BODLEY SCOTT said that the pieces of bone marrow showed megaloblasts, which had never before been produced in animals. He had worked out that the dose of anahæmin used was equivalent to the administration of 90 cc to a human being, and wondered what the effect of a more proportional dose would have been.

DR W S C COPEMAN asked whether the possible intestinal toxæmia had had any other effect, on the locomotor system for example.

DR W RITCHIE RUSSELL asked whether the animals showed evidence of neuropathy or encephalopathy.

DR WATSON replied that the animals lost weight, but showed no other signs of deficiency disease. They had no diarrhoea, but he was not certain that they had no steatorrhoea. He did not claim that the bone marrow showed megaloblasts, because no one knew what a megaloblast in an animal would look like. He had not tried a proportional dose of anahæmin, but he felt that there was not necessarily a quantitative relationship between the dose and the weight of the animal. No evidence of neuropathy had been observed, but the neurological investigation of rats was a little difficult. Up to the present no histological investigations on the brain and cord had been done.

3 DR R W D TURNER, in describing the *Carotid Sinus Syndrome*, said that a man aged 61 years, with benign essential hypertension, complained of frequent incapacitating

attacks of giddiness which were shown to be due to hypersensitive carotid sinus reflexes. Pressure over either sinus resulted in immediate cardiac asystole. Bilateral carotid sinus denervation was carried out and during the succeeding 16 months the patient had been free from his previous attacks and there had been no adverse effects from the operation. Although a number of cases of unilateral carotid sinus denervation had been reported, there had been very few in which the operation had been carried out on both sides, presumably through fear of possible adverse effects on the heart and circulation. The case was described in detail, together with an outline of the physiological and anatomical basis of the syndrome.

Dr G. J. LANGLEY congratulated Dr Turner on having read Hering's paper, the most appalling medical paper ever written, of which Dr Langley could never make any sense.

Dr I. T. FREEMAN remembered that Charcot's laryngeal syndrome had been described at an earlier Meeting of the Association, and he wondered whether this was related to carotid sinus ischaemia. He instanced three cases of patients who collapsed on coughing, but recovered in a few seconds as though nothing had happened, and suggested that although it was not often recognized, it was not an uncommon condition. As one of the patients had been a taxi-driver, who had attacks while driving, he felt that the disease had acquired a new significance, and he wondered whether the fashion for wearing tight soft collars was responsible for the recrudescence of a disease which had been described by Charcot, when men wore stocks.

Dr HUGH BARNER remembered the communication on laryngeal vertigo. He suggested that it would be interesting to try the effect of pressure on the carotid sinus in patients liable to laryngeal vertigo.

Dr W. R. SNOODON said that pressure had been tried in these cases, but that it had no effect.

Dr RAE GILCHRIST thought that laryngeal vertigo was a different condition. He had seen a case of laryngeal vertigo in an elderly man with whooping-cough, in whom the attacks had been diagnosed as Stokes-Adams disease. The carotid sinus syndrome could be produced by pressure on the sinuses, but he agreed that pressure does not cause syncope in cases of laryngeal vertigo.

Dr TURNER, replying, modestly confessed that he had not read Hering's paper in the original German, but a paper in English which referred to it. He agreed that laryngeal vertigo was a separate condition, and thought that it would be worth adopting the suggestion of trying a different type of collar in cases of carotid sinus syndrome.

4 Dr D. C. WATSON (introduced) and Dr H. S. PEMBERTON described the use of *Nitrogen Mustards in the Reticuloses*. They presented a clinical study of nine cases treated by nitrogen mustards. They pointed out that these substances were powerful poisons, but that their chlorides freshly prepared, were easily soluble in water and could be administered in a saline infusion. They had given a dose of 0.1 mg. per kilogram of body-weight, daily for four days. Administration was liable to be followed by immediate toxic effects consisting of malaise, anorexia, nausea, and vomiting, and by delayed effects due to depression of the bone marrow. This manifested itself by a fall in the number of white blood corpuscles, sometimes amounting to severe granulopenia; nitrogen mustard had no effect on the red blood corpuscles. Five cases of Hodgkin's disease had responded well, both in respect of glandular enlargement and symptoms. Improvement started two to five days after a course and lasted for up to nine months. Early cases did best. Previous irradiation did not seem to affect the response. Cases with sarcomatous changes showed a response much less satisfactory in degree and duration.

Dr PEMBERTON asked Dr J. F. WILKINSON, as an authority on the subject, to say a few words.

Dr WILKINSON said that nitrogen mustard had been introduced as a therapeutic agent as a result of observations made during the war on workers manufacturing alkylamines. Attempts had been made to apply the treatment to leukaemia, but for security reasons he had been forbidden to publish the results. The details were, however, sent to America as part of the inter-allied co-operation, and the results had been published there. He thought it was a hopeful line of treatment both for myeloid leukaemia and Hodgkin's disease. He had obtained similar results to those reported by Dr Watson. He had found that the immediate toxic effects could be controlled by sedatives, specially if the total dose was restricted to 4 or 5 mg. and doses were given every second or third day. By this means it was possible to treat patients as out-patients. Some of the cases he had treated had remained well for years, but he felt that physicians should be reminded to

stop the treatment in cases of leukaemia when the white cells had fallen to 30,000 per c.mm., because the fall continues after the cessation of treatment. He pointed out that the white blood cells were not nearly so sensitive in Hodgkin's disease.

DR R. BODLEY SCOTT had used nitrogen mustard in 25 cases, of which 12 were of Hodgkin's disease, but his results on the whole had been less satisfactory. He thought that X-rays were more reliable for the urgent relief of swelling, but that in late cases with diffuse enlargement and bone pains, nitrogen mustard was sometimes wonderfully effective. He had found that the immediate toxic effects were sometimes controllable by doses of 100 mg. of pyridoxine.

DR DAVIES had not found that treatment reduced the blood sedimentation rate, and asked what Dr. Watson's experience had been.

DR WATSON, replying, said that nitrogen mustard had been very effective when relief of swelling was urgently needed in a case of large mediastinal glands, and that the blood sedimentation rate had fallen to normal in the three of his cases on which he had made observations.

5 PROFESSOR HENRY COHEN, describing *Some Unusual Xanthomatous Lesions*, presented four cases which shed light on some of the problems associated with xanthomatosis. The first was a child of five years with a three and-a-half-years' history of illness, with a normal cholesterol content of the plasma. Clinically there were generalized bone lesions, xanthoma tuberosum, some lymphnode enlargement, miliary pulmonary lesions, and a profound anaemia. Post-mortem histological examination showed lesions consistent with histiocytic sinus reticulosis (Stengel-Wolbach) with giant cells, eosinophilic granuloma, the Letterer-Siwe syndrome, and the classical foam cells of the Hand-Schüller-Christian syndrome. There were also areas showing resolution with fibrosis. Professor Cohen suggested that despite the varied and confusing nomenclature of the xanthomatoses they represented a unitary pathological process. The second case showed advanced myxoedema with hypercholesterolaemia and xanthomatosis of the palms, treatment with thyroid extract had resulted in a disappearance of the xanthomatous lesions. The third group of cases illustrated the xanthomatoses accompanying familial coronary occlusion. The fourth case showed the transition of xanthoma planum into calcinosis cutis.

Annual Dinner

The Annual Dinner was held in the Adelphi Hotel and was attended by 170 members and guests. The President, PROFESSOR JOHN HAY, was in the Chair. The toast of the Association was proposed by the President. That of the guests was proposed by PROFESSOR R. PLATT, and the Most Reverend the ARCHBISHOP OF LIVERPOOL replied. The toast of the President was proposed by DR A. P. THOMSON. The Dinner was, in all respects, an outstanding success.

Saturday, 10 a.m., Morning Session

1 DR E. E. POCHIN described the work on *The Investigation of Thyroid Function by Radioactive Iodine*, which he had done with N. B. Myant and the late E. A. G. Goldie. He said that when radioactive iodine (I_{131}) is given by mouth to normal subjects, the rate of its uptake by the thyroid and excretion in the urine can be followed using Geiger counters. Each of these rates has fallen to a low value within 48 hours. In thyrotoxic subjects, a given dose is more completely and much more rapidly taken up by the thyroid, owing to the greatly increased rate at which the thyroid clears iodide from the blood-plasma. The values for plasma clearance have been increased by over tenfold in the thyrotoxic as compared with normal subjects, and this measurement appears to offer a hopeful method of investigation of thyroid function.

PROFESSOR HENRY COHEN described the work done by Dr. Ansell of the Department of Medicine and Dr. Rowplatt of the Department of Physics on the recognition of retrosternal goitre by I_{131} . He showed diagrams of the special counter used for the purpose, and demonstrated how accurately the counter could mark out on the skin the position of a retrosternal iodine retaining goitre.

DR S. H. COOKSON said that it is important that the thyroid should be as free of iodine as possible. Presumably the patient should not have had iodine administered for some time previously, and he asked what was the minimum time of freedom from medication for the test to be effective.

DR A. W. D. LEISHMAN asked whether nodular goitres responded in the same way as the diffuse type.

Dr POCHIN replied that data were being collected about the relation of the administration of iodine to the efficiency of the test. He said that radioactive iodine could be washed out of the thyroid by a large dose of Lugol's solution. He had no data so far about nodular goitres.

2 Dr J C HAWKLEY made some *Observations on Erosions of the Stomach*. He said that in many cases of gastrostasis the clinical diagnosis can only be made by inference. Erosions are known from examination of post-mortem material and stomachs resected at operation, they may be seen by a gastroscope and have been well studied through gastric fistulae by Beaumont and by Wolf and Wolff. Linhorn, finding pieces of gastric mucosa in wash-water from certain stomachs, accepted this as evidence of erosion. The speaker had found similar pieces in 10 per cent of samples of aspirated resting juice from cases with gastric symptoms, mostly due to ulcer. Nearly all specimens showed the histological changes of advanced gastritis. He had had one instance of the shedding of a carcinomatous flake presumably from an erosion near a carcinoma. These pieces demonstrate anew the ease with which detachment of fragments occurs from diseased gastric mucous membrane.

Dr F AYTON JONES said that in the post mortem of a case of erosions in a child who had died of diarrhoea and vomiting, no infiltration was found around the erosions. It appeared that in this case little pieces of mucous membrane had just dropped out. He had found the same thing *post mortem* in a man aged 85 years. He thought that erosions were not necessarily caused by gastritis.

Dr E G L BYWATERS wondered how long the fragments had been separated and how long it would take for them to be digested by the gastric juice.

PROFESSOR J W MCNER questioned the frequency of hypertrophic gastritis. He had found it rare, though the literature suggested that it was common. He asked how often fragments representing erosions were found in relation to hypertrophic gastritis.

PROFESSOR L S P DAVIDSON said that in 40 out of 100 of his patients, no diagnosis had been made of the cause of haematemesis. They were not X rayed until two or three weeks after the bleeding, and he wondered whether this was the reason why the barium meal showed no abnormality.

DR S J HARTFALL thought that hypertrophic gastritis was rare. The thickened mucosa so often called hypertrophic gastritis was only one of the manifestations of the duodenal ulcer diathesis.

DR D M F BATTY had found that punch biopsies carried out through a gastroscope had not confirmed the gastroscopic impression of hypertrophic gastritis.

PROFESSOR CLIFFORD WILSON commented on the relation of erosions to undiagnosed haematemeses.

Dr HAWKLEY, replying, said that he had not investigated the digestion of fragments by gastric juice, because that would have lost them for histological examination, but physiologists had expressed the opinion that they would be digested rapidly. He had found that hypertrophic gastritis was a rarity, though evidence of it was sometimes found in the fragments of mucous membrane. He thought that everyone had had experience of haematemeses in which the cause could not be diagnosed. In America such cases had been gastroscopied early and found to show evidence of erosion. Culture of the fragments in five cases produced only flora associated with the normal pharynx, and there was no histological evidence in the cells of their having been invaded by a virus.

3 Dr O FITZGERALD discussed *The Influence of Urea on Gastric Acidity*. He said that urease was known to be present in the mucosa of the stomach of all animals investigated, including man. It was capable of breaking down urea to form ammonia. More urease was present in superficial than deep mucosa, more in the upper than in the lower stomach, and far more in either than in the duodenum. In quantitative terms enough was present to release sufficient ammonia for neutralization of the usual amounts of acid formed. There was an obvious theoretical relationship between the urease present and gastric neutralization and mucosal protection. Urea administered to normal human subjects caused a consistent decrease in their response to histamine, associated with some rise in gastric ammonia and apparently little change in the volume response. He suggested that this effect was due to increased neutralization. The rise in blood-urea was slight and within the physiological range. This effect might possibly occur normally after a meal, in uraemia, and as an explanation of the improvement in ulcer symptoms after a haemorrhage. He discussed the therapeutic use of urea for peptic ulcer.

4 DR R S ALLISON, discussing *The Effect of Diet and Regular Living Conditions on Men with Peptic Ulcer*, said that in the Royal Navy, during the war, 63 men with proved peptic ulcer were kept under ideal working and dietetic conditions for a year. Obviously neurotic and unstable types had been rejected and the group as a whole were of superior intelligence. Surprisingly little working time was lost through recurrence of dyspeptic symptoms. Three quarters were off work for a week or less and only nine (14 per cent) were off work for more than three weeks during the year. That this was due to their will to work rather than to rapid healing of their ulcers was shown by the results of re-examination at the end of the test period. Though three quarters claimed to be symptom free, there was persistent radiological abnormality in half the number. Only one tenth were free of all symptoms and signs of gastroduodenal dysfunction. Though co operation had been good and such recognized causes as irregular meals and indigestible food eliminated, there was no evidence to suggest that length of history, previous complications, or smoking and drinking had any material effect on the results. As a whole, these findings challenged the validity of many so called causes of chronicity and recurrence in ulcer, as also the necessity of devising elaborate medical régimes for cure.

5 DRS W R S DOLL (introduced) and F AVERY JONES described their *Observations on the Occupational Incidence of Peptic Ulcer*. They said that 6,047 men and women engaged in different occupations had been interviewed. The incidence of peptic ulcer in men rose to a maximum of 9.6 per cent between the ages of 45 and 55 years, falling at later ages. Duodenal ulcers were found to be evenly distributed among the Registrar-General's social classes, but gastric ulcers were rare in Classes 1 and 2 and common in Class 5. A marked excess of ulcers was found among medical practitioners, this could be attributed to better diagnosis. A possibly significant excess was found among men holding responsible positions in industry, executives and foremen. The incidence of ulcer among agricultural workers was low. No evidence was obtained of any abnormal incidence among bus drivers or conductors.

THE PRESIDENT asked whether the family history showed any familial tendency to peptic ulcer.

DR C R NAISH said that the Bureau of Health and Sickness Records in the Department of Social Medicine at Oxford related the hospital figures to the population. An analysis of three years' records of peptic ulcers in hospital amongst insured men showed that the highest rate was in indoor brain workers, the next highest in indoor industrial workers, and the lowest in outdoor workers. He suggested that in some inexplicable way outdoor work seemed to protect from peptic ulceration.

DR AVERY JONES thought that we had little knowledge of the factors that we think are significant. He suggested that gastric and duodenal ulcer were really different diseases. He said that his experiences had confirmed Dr Allison's, and that he felt that the disease was more important than the factors militating against it.

DR S ALSTEAD asked whether Dr Doll's figures related to town or country, and suggested that it would be interesting to investigate the incidence of ulcers among rural doctors, a group of brain workers who live largely in the open air.

DR S J HARTEALL asked what criteria had been taken for the diagnosis of peptic ulceration. It was possibly a fallacy to include cases of ulcers with symptoms, but not to investigate patients without symptoms, because it was known that some patients with ulcers were completely free of symptoms.

DR HUGH BARBER commented that there had been no mention of shift work. His own impression was that there was a relation between shift work and peptic ulceration.

DR T E GUMPERT said that people often say that they have an ulcer and wondered whether Dr Doll had verified these statements.

DR H K GOADBY said that the capacity of a patient to keep on working depended mainly on the personality of the doctor, and suggested that what Dr Allison's figures really proved was that Dr Allison was a better doctor than the average doctor in Scotland.

DR J S T C ELKINGTON asked whether Dr Allison had followed his service cases since their return to civilian life.

DR ALLISON, replying, said that the men were not under his personal care and that it was the will of the men to work and not driving by others which was the important factor in securing a low incapacity rate from recurrence of symptoms. He had not followed his cases into civilian life, but hoped to make the attempt. He thought that Dr Doll

was right in stressing the significance of the personality of the patient in determining the extent of his symptoms and suggested that in using medical practitioners as statistical material, one should take into account that doctors were more aware of their own symptoms and of their significance than the general run of the population

Dr Dorr, replying, said that his diagnoses had been based on operation or X rays in the past. The X ray criteria were a crater or deformity, and the diagnosis had been verified as having been made in a hospital. He agreed that he could not have obtained a complete picture of the incidence of ulceration, because there were symptom free ulcer subjects. He had found that the incidence was the same in outdoor workers in towns as in indoor town workers, but said that he would investigate the doctors in a rural division of the British Medical Association. He had found no significant relationship between shift-work and the incidence of ulcers. He had found a strong family history in patients with ulcers.

6 Dr N C OSWALD gave a description of *Honeycomb Lungs*. He suggested that the term honeycomb lungs can best be applied to cases showing emphysematous bullae scattered uniformly throughout the substance of both lungs. Eighteen such cases had been collected and these, together with a further 16 from the literature, showed two predominant clinical characteristics, namely, spontaneous pneumothorax, frequently bilateral, and right heart failure, which was often initiated by an attack of bronchitis, and terminated fatally in about two years. Five of the cases fell under the general heading of reticulosarcoma. Eleven cases fell into the group of tuberculous sclerosis and allied disorders (myomata, &c.) A further five cases, four of which had diabetes insipidus, suggested association with pituitary disorders. The remaining 11 showed no evidence of a general affection, the lungs having varying degrees of interstitial fibrosis.

Dr J. L. LIVINGSTONE suggested that although honeycomb lung was a rarity, one should always think of the possibility in a case of spontaneous pneumothorax. When it was found, it was worth considering the production of pleural adhesions as a preventive measure. He commented on the oddity that the bronchograms are so normal in so abnormal a lung, and on the fact that bullae of this kind are not found in asthma, although one would expect them.

Dr L. H. HUDSON asked whether the patients had any symptoms other than pulmonary ones.

Dr J. G. SCADDING said that in these cases obstructive lesions in the bronchioles had not been found, but might have been present. The cysts were the result of the distension of ultimate lobules of lung tissue, and only a small proportion of the terminal bronchioles need be affected to produce this appearance. A little swollen tissue at the right point was certainly a possible mechanism for the production of cysts. He suggested that the cysts were related to a congenital anomaly, but were not necessarily inborn, but subsequently acquired. Such cysts could be produced in a great many different ways.

PROFESSOR L. J. WITTS asked what was the differential diagnosis between this condition and congenital cystic disease. He suggested that these cases, although they were not congenital, were genetically determined.

Dr H. H. MOLL suggested that there was a familial incidence, and that the disease was transmitted to males.

Dr T. L. GUMPERT asked why the spontaneous pneumothorax was so often bilateral. Did it mean that two bullae ruptured simultaneously, or that the air welled through the mediastinum?

Dr OSWALD replied that the symptoms spontaneous pneumothorax and dyspnoea often followed an attack of bronchitis. He said he was making further investigations for obstructions in the walls of the smaller bronchioles. He suggested that the characteristic of so called congenital cystic disease was that it affected only part of one lung. There were cases in young infants with cysts like bunches of grapes which were truly congenital. He suggested that the reason the pneumothorax was so often bilateral was because as soon as it occurred on one side, the added strain of respiration caused the rupture of a bulla in the other lung.

At 1 p.m. Members lunched at the Medical Institution.

At the conclusion of the Meeting the Association expressed its thanks for a most happy and successful occasion to Professor J. Hay and to all the Liverpool members, particularly Dr R. W. Brookfield and Dr H. S. Pemberton.

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